Studies on Codeine Addiction

By

By

C. K. HIMMELSBACH, HOWARD L. ANDREWS
ROBERT H. FELIX, FRED W. OBERST
and LOWREY F. DAVENPORT

FOREWORD

Among the problems which are being studied in the research unit of the Lexington hospital, and by cooperating groups that have been seeking a solution of the addiction problem, is the role of codeine as an addicting drug. The work reported here represents the co-ordinated effort of clinical and laboratory workers who have studied the subject from different angles so that the effect of codeine could be viewed as a whole and in proper perspective with the effect of other opium derivatives.

There has been much difference of opinion among clinicians as to whether codeine could produce addiction comparable to that pro-duced by morphine. The freedom with which this drug has been used in medical practice without apparent harm and the overshadow-ing importance of addiction to other opium preparations have tended to cast doubt upon the genuineness of the few reported cases of addiction to it. The report of this group of workers clears up some apparently contradictory evidence and is a valuable guide to those who would use codeine with maximum benefit and minimum danger to the patient.

Physical dependence with consequent spectacular abstinence syn-drome is the most striking thing about opiate addiction. It is the reaction that is feared by both physicians and patients, but it is not the most important thing from the standpoint of continued addiction. The dependence studies of this report, showing that codeine supports physical dependence produced by morphine, and the 25 reported cases that exhibit the abstinence syndrome, prove beyond doubt that codeine brings about physical addiction. The behavior studies show why, in spite of this, there are so few codeine addicts.

The basis for continued addiction to opium is the psychic satis-faction derived from the use of the drug. Codeine, as a rule, gives very little, if any, psychic satisfaction, and the potential addict, annoyed by physical dependence that is not compensated for by mental ease, turns from it in disgust. The drug is dangerous, how-ever, since, once physically addicted, he may turn to more gripping drugs. It is important to know this and to have demonstrated the fact that smaller doses than are usually prescribed are sufficient to control coughs.

These findings, together with the demonstration of the effect of codeine on the electrical potentials of the cerebral cortex, the com-

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parison of these potentials with those associated with the use of morphine, the determination of the percentage of codeine intake that is excreted in the urine under varying conditions, and the description of a method for actually measuring the amount excreted are important steps in our progress toward a more complete understanding of the striking reactions of the human economy in its efforts to adjust to the repeated insults of large doses of opium. Better methods of prevention and treatment will inevitably follow such understanding, and this work as a whole is a significant contribution toward the desired goal.

LAWRENCE KOLB,
Assistant Surgeon General,
Division of Mental Hygiene, United States Public Health Service.

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PART I. A REVIEW OF THE LITERATURE ON CODEINE ADDICTION

By C. K. HIMMELSBACH, *Passed Assistant Surgeon, United States Public Health Service, United States Public Health Service Hospital, Lexington, Ky.*

In view of the fact that there are conflicting opinions concerning the addiction liability of codeine, it seemed desirable to review the literature so as to gain information on the significance of codeine as a drug of addiction.

This review, although not complete, covers the bulk of the literature pertinent to the subject. The recent reports of Davenport (*1*) and Wolff (*2*) also contain reviews of the incidence and significance of codeine addiction.

Clinical Literature

In 1905, Pelz (*3*) reported what is probably the first case of true addiction to codeine. In this case the drug was originally prescribed in 30-mg. doses to be taken 3 times daily for "nervousness." Since this did not give relief, the patient took about 1 gram by mouth and experienced a profound sense of relief and well-being. He then took large amounts, averaging about 1.5 gm. per day orally, for several months before taking his first abortive cure. He relapsed in a few days, and within a year was taking up to 3 gm. of codeine per day. About 2 years later he was treated by the method of abrupt and complete withdrawal. Pelz's description of the abstinence syndrome exhibited by this patient indicates that he had developed definite physical dependence upon codeine.

In 1913, Sollier (*4*) reported a case of an elderly patient who took codeine regularly for rheumatic pains, and within 3 years reached a daily dosage of 2 gm. In treating this case the drug was withdrawn rapidly in 8 days. This is significant, since Sollier favored abrupt withdrawal in all but severe or debilitated cases. Sollier's description of the abstinence syndrome indicates that this patient had developed strong physical dependence upon codeine.

In the same year, Petty (*5*) asserted that codeine could be used without producing addiction for longer periods than could other opium preparations. However, he did not state that he had actually observed any cases of codeine addiction.

In 1914, Lambert (*6*) stated that he had seen a few cases of codeine addiction, and in 1922 (*7*) he reported that he had treated a total of 17 cases. No further reports have been made by Lambert.

In 1921, the Committee on Narcotic Drugs of the Council on Health and Public Instruction of the American Medical Association recommended that that Association urge Congress to amend the Harrison Narcotic Act to permit physicians to prescribe codeine without restrictions. The Committee felt that rarely, if ever, did codeine lead to the development of addiction (8). However, they must not have considered codeine to be entirely devoid of addiction liability, for they stated, "Morphine and heroin should not be used for symptoms which may be relieved by codeine or other less actively habit-forming drugs."

In 1922, Watson (9) reported the results of a questionnaire which showed that no case of codeine addiction had been encountered in Maryland. He, too, felt that codeine should not come under the scope of the Harrison Narcotic Act.

In 1924, Rouges de Fursac and Monestier (10) reported a case of true addiction to codeine. In this case the drug was originally prescribed in 30-mg. doses to be taken by mouth during asthmatic attacks. The patient obtained positive euphoria from the first dose. At first she took the drug only during the attacks, but she began to look forward to the next one because of the pleasure obtained from the prescription. After about 5 years she completely succumbed to the seductive influence of codeine and took it at the slightest pretext. Later, she began to increase the dose, and then gradually to increase the frequency of administration. Finally, after about 6 years of increasingly regular use, she began to take 0.5 gm. per day. Six months later her family became alarmed and, as a result, she attempted to discontinue the habit. The appearance of characteristic withdrawal symptoms caused a prompt relapse and in a short time she increased the dose to about 1.0 gm. per day. About 2 years later she was persuaded to undergo formal treatment. Even though the drug was withdrawn by reduction (10 days), phenomena of drug deprivation appeared. The authors were convinced that the patient had developed definite physical dependence upon codeine, but considered the dependence to be less intense than that usually seen in morphine addition.

In 1927, Terry (11) reported the important features of 2 cases of codeine addiction which had been described to him by a Montgomery, Ala., physician. The first case had used codeine for about 12 years. During one year he was known to have used an average of 11 grains (0.715 gm.) per day. The other case had been taking codeine hypodermically for about 7 years. During the last year the daily dose was about 4 grains (0.260 gm.). Both patients exhibited deprivation phenomena described as identical with those encountered when morphine is withdrawn from morphine addicts. An El Paso, Tex.,

physician told Terry (*11*) that he had seen one case of true codeine addition and that he had frequently observed restlessness following withdrawal of codeine after its prolonged administration.

In 1928, Ashworth (*12*) expressed the belief that codeine should be considered an addicting drug. Although he did not report any cases of codeine addition, his statement bears repeating: "It is, of course, obvious that the continued use of codeine itself invites the use of morphine or other opiates * * *."

In the same year, Joël (*13*) stated that he had seen one case of pure codeine addiction; however, no description of this case was given.

In 1930, Adams (*14*) conceded that the possibility of codeine addiction had been proved, and that the medical use of codeine appeared to be increasing, but pointed out that addicts greatly prefer morphine and heroin.

In the same year, Schwartz (*15*) reported 3 cases of pure codeine addiction which he had treated. The daily dosage of codeine for each of these patients was 3.0 gm. Although the duration of codeine abuse by these patients is not stated, the inference is gained that one used the drug for about 5 years and the others for only about 1 year. The signs and symptoms which appeared in these patients following withdrawal of codeine were as intense and prolonged as those usually seen following withdrawal of morphine from morphine addicts.

Later in 1930, Bonhoeffer and Schwartz (*16*) called attention to several features which operate against a higher incidence of codeine addiction: The euphoria is slight compared to that of morphine and heroin, and the size of an effective dose is much larger and more expensive than that of morphine and heroin.

In the same year, Heimann-Hatry (*17*) reported an experience with a patient who was using codeine, presumably to satisfy addiction. However, the author did not treat this patient during withdrawal and never saw her after his second prescription for codeine had been raised.

At the Narcotic Drug Conference held in Washington in 1930, Doctor Woodward stated that in the replies to questionnaires sent to physicians in Ohio several cases of codeine addiction were reported. Doctor Woodward (*18*) made this significant statement: "The testimony of one man that he has seen a codeine addict is much more valuable than the testimony of a thousand men that they never saw one."

In 1931, Terry (*19*) reported that a considerable number of persons in and around Detroit, Mich., were using codeine regularly and in excessive amounts. A study of the narcotic prescriptions showed that in a number of instances the first prescription was for codeine

in therapeutic amounts; next came orders for larger amounts at shorter intervals, and finally for addiction-sustaining amounts of morphine, heroin, or opium. This sequence of events is consonant with the view expressed by Ashworth (12).

In 1932, Foley (20) reported the case of a patient who took codeine every day for a period of about 4 months for asthma and "abscesses." The initial dosage was 2 gr. (0.13 gm.) daily, and during the last month this was increased to 4 gr. (0.26 gm.). The drug was withdrawn in 7 days with mild attendant abstinence signs and symptoms. The patient relapsed within a week and used 4 gr. (0.26 gm.) of codeine per day for the next 4 months. Again the drug was withdrawn by reduction in one week, but no mention was made of abstinence phenomena. Experience with many addicts makes one wonder about the cause of the "abscesses" in this case.

Sollmann (21), in 1932, stated: "Codeine addiction is rare and generally easily broken. Its narcotic action is so slight that it is not very tempting to addicts, and really narcotic doses would be inconvenient to administer, and disproportionately expensive, so long as its sale is restricted. If restrictions were removed, however, so that it could be procured in unlimited quantities, the situation would doubtless become very different."

Meyer (22), in 1933, reported that he had seen 3 patients who were addicted to codeine. Two cases were women who became addicted to codeine and used it exclusively. One of them took codeine in steadily increasing doses for 3 years, and the other had used it regularly for 10 years. The third case, a very intelligent chauffeur, had used codeine steadily, but not exclusively, for 7 years. This patient stated that, although he had tried many types of morphine preparations, none gave him the pleasant sensations produced by codeine. No information was published on the treatment of these cases.

Adams (23), in 1934, related the case of an elderly patient who had used about one ounce of codeine per week for 17 or 18 years. She poured an unmeasured amount of powder in the palm of her hand and licked it off each morning and evening. No withdrawal was attempted and the patient died of heart failure.

In 1934, Light (24) stated that he had seen several cases of codeine addiction, but none of these was described, and the author considers the condition to be rare.

In 1935, Chodzko (25) described in detail the first case of codeine addiction reported in Poland. The case history and findings were obtained from a report by the patient's physician, Dr. J. Krasowska. This patient had been using codeine regularly for a year, the dosage increasing steadily to 1.2 gm. per day. The patient had attempted to abstain, on several occasions, but was unable to complete the denarcot-

ization because of intense withdrawal symptoms. The abstinence syndrome exhibited by this patient following abrupt withdrawal is described in great detail, and indicates that strong physical dependence upon codeine had been acquired.

Codeine addiction in almost epidemic proportions occurred in Canada about 1933. Canadian importations [1] of codeine rose from 311 kg. in 1926 to 724 kg. in 1929, and to 1,040 kg. in 1933. In 1933 the codeine consumption in kilograms per million inhabitants was 109 as compared with 29 in the United States, 11 in Great Britain, and 4 in Australia, all racially comparable countries. Sharman (26), the Canadian representative to the League of Nations Advisory Committee on Traffic in Opium and Other Dangerous Drugs, stated, "From all parts of Canada there is indisputable evidence that addicts are experiencing considerable difficulty in obtaining their drug of addiction, and many are known to be 'carrying on' with codeine." He described one case who used 0.9 gm. of codeine per day intravenously, and showed characteristic deprivation phenomena when codeine was withheld (27). In 1935, Sharman (28) stated, "The Canadian authorities are experiencing much trouble with codeine addiction. There are 34 cases in the hospitals of one province, and in some cases the doses administered by hypodermic needles amount to as much as 80 gr. (5.2 gm.) per day."

In the same year, Slight (29) described 3 cases of codeine addiction which he had treated in Montreal. The first was a young woman who had been using codeine regularly for 2 years. She started with 2 grains (0.13 gm.) a day and was taking 40 grains (2.6 gm.) each day intravenously at the time treatment was instituted. The abstinence syndrome which followed withdrawal of codeine was in every way characteristic, but somewhat less severe than the syndrome of morphine withdrawal. The second was a former morphine addict who, after a year of abstinence, had relapsed to codeine. Starting with 5 gr. (0.325 gm.) per day, within two months the intravenous daily dosage had reached 80 gr. (5.2 gm.) of codeine. The abstinence syndrome which occurred following withdrawal of codeine at this time was characteristic of, but milder than, morphine abstinence. The third case was a young woman who had been taking 30 gr. (1.95 gm.) of codeine by mouth daily for an unknown period (probably less than 3 years). The abstinence syndrome exhibited by this patient was severe.

The fact that Canadian addicts recognized codeine to be an addictive drug is borne out by the following letter which was reprinted in the Canadian Medical Association Journal of July 15, 1935:

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[1] No narcotics are manufactured in Canada.

EDITOR, SUN:

SIR: Recently I have cured myself of a 2-year narcotic habit, or, in the parlance of those addicted to any habit-forming drug, have "kicked a tough habit." Believe me, it would be impossible to convey to anyone the mental torture along with the physical pain and torment that unites to make this one of the worst ordeals that a human could endure.

Every now and then I read in your paper of some poor character arrested, tried, and punished for the possession of a narcotic in some form. Strange to say, a drug is purchasable in nearly all the city drug stores. I refer to the drug, codeine. Lately there has been a slight stir in legal circles to ban, or rather enter this drug on the poison list—that's all, just talk. Codeine, while not being equally as strong as morphine, heroin, or opium, can be injected hypodermically in the human system in a vaster quantity, thereby making it a more insidious evil.

I could devote pages to describe the effects, but suffice to say it is every bit as habit-forming as the drugs above mentioned, and racks the system to a greater extent than a stronger drug * * *.

Now, don't you think, Mr. Editor, this evil should be stamped out? It is surprising the many youngsters that are indulging in this dangerous pastime.

You will not credit it, but just the other day I saw a young couple, the lad could not be more than 20 years old, and the girl the same age, making a purchase of codeine. This is where our new civic administration could really do some good.

I am just an old reprobate trying to do a good act.

<div align="right">OLD REP.</div>

NOTE: This is a clipping from the Vancouver Sun, kindly sent us by Col. C. H. L. Sharman of Ottawa. It will be of interest to our readers in connection with the campaign against codeine addiction. (Editor.)

In 1935, the Canadian Government indicated that it had become officially aware of the fact that codeine was being used in large quantities for addiction purposes within the Dominion (30), and in 1937 reported that this situation was showing considerable improvement (31). The improvement was attributed to amendments in the Pharmacy Acts of Manitoba, British Columbia, and Saskatchewan, through which codeine was made available only upon physicians' prescriptions, and which limited retail druggists to 1 ounce per month. Reductions in the amounts of codeine used in other Provinces were also noted, but these were not comparable to the reductions which resulted from amendments of the Pharmacy Acts.

In 1935, Treadway (32) prepared a Memorandum on Codeine Addiction for the use of Mr. Stuart J. Fuller, at the Opium Advisory Committee Meeting in Geneva during that year. This memorandum contains abstracts from the official United States Government records of 18 bona fide cases. The first 5 cases were former morphine addicts who had completely substituted codeine for morphine in attempts to relieve themselves of their addiction. The next 4 cases became addicted primarily to codeine and did not use other drugs. Each became physically dependent upon codeine and one relapsed to it

following treatment and induced her husband to use it. The records indicate that he, too, became addicted to codeine, but no separate description of this case was given.

The next 5 cases were former morphine or heroin addicts who, being unable to obtain their preferred drugs of addiction, switched to codeine and were apprehended smuggling the latter drug from Canada. All were hospitalized and all showed characteristic deprivation phenomena.

The last 4 cases, also apprehended smuggling codeine from Canada, were primary codeine addicts, who used this drug to the exclusion of other drugs. All exhibited characteristic abstinence phenomena upon withdrawal of codeine, and two of them later relapsed to codeine addiction.

In 1936, Ostromislensky (33) reported that he had treated 3 cases of codeine addiction, and that no severe withdrawal symptoms were observed. Since these cases were treated with "Rossium," a pyrazolone derivative which has been shown to be ineffectual in ameliorating abstinence signs and symptoms (34), it must be assumed that they had not developed strong physical dependence upon codeine.

TABLE 1.—*Reported instances of codeine addiction*

Definite [1]	Presumptive [2]	Author
1	--	Pelz.
1	--	Sollier.
--	17	Lambert.
1	--	Rouges de Fursac and Monestier.
2	1	Terry.
--	1	Joël.
3	--	Schwartz.
--	1	Heimann-Hatry.
--	[3] 3	Woodward.
--	1	Foley.
--	3	Meyer.
--	1	Adams.
--	[3] 3	Light.
1	--	Krasowska and Chodzko.
--	34	Sharman.
3	--	Slight.
13	6	Treadway.
--	3	Ostromislensky.
25	74	

[1] Description of abstinence syndrome given.
[2] No description of abstinence syndrome given.
[3] Author reported "several" cases.

A summary of these reported cases of codeine addiction is given in table 1. It will be noted that there have been found 99 cases of codeine addiction: 25 cases are considered to have been definite, and 74 presumptive. It is likely that some of the cases listed as "presumptive" could have been classed as definite if descriptions of the signs and symptoms following withdrawal of codeine had been given

by the authors. More than 20 percent of these cases appear to have been primarily and exclusively addicted to codeine, whereas in about 50 percent addiction to codeine was probably secondary to or superimposed on addiction to other drugs. The histories of about 30 percent of the cases were vague on this point.

Animal Experimentation

From experiments carried out on monkeys, Kolb and DuMez (35) concluded that codeine has very little dependence-producing power as compared with morphine and heroin. In one instance these investigators were unable to satisfy with codeine physical dependence developed to morphine, which had been sustained for 75 days by heroin. Only suggestive withdrawal signs were observed in three monkeys that had been given codeine (40 to 80 mg. per kg. per day) for 6 to 9 months. Five animals died during the addiction period, and injections had to be discontinued in another animal because of the progressively toxic effect.

Seevers (36) encountered similar difficulties in attempting to produce codeine addiction in monkeys, and offered the following explanation: "The convulsant action of the drug prevents the attainment of doses which, on the basis of their relative clinical effectiveness, are in any way comparable to those which may be reached in the human subject." This, he feels, makes the monkey an unsatisfactory laboratory animal for studying codeine addiction.

Recently, through the courtesy of Mr. Kusama [2] and Colonel Sharman,[3] we have seen a film entitled "Chronic Codeine Habituation of Monkeys," photographed by Dr. K. Nishida and directed by Professor K. Abe, of the Laboratory of the Department of Pharmacology, Medical College, Keio University, Tokyo, Japan. This film depicted the successive phases of addiction and abstinence in a monkey that had been given 0.99 grain (0.198 gr. per kilo) per day for 408 days. Kolb, after viewing this film, stated:

I found monkeys very intolerant to codeine phosphate. Because of the deleterious effect of the drug, five animals in a series of nine that were given small but increasing daily doses died in from 15 days to 6 months after injections were started. The largest total daily dose that any of the nine received was 0.042 gm. (0.65 gr. per kilo) given in two injections, but the amount had to be reduced to 0.015 gm. (0.23 gr. per kilo) in order to keep this animal alive for 1 year.

Five of the nine animals that were given codeine by me lived 6 months or more and were tested for abstinence symptoms on several occasions. All of them were given for several months from two and one-half to more than three times the dose received by Professor Abe's animal, but only two of them showed

even a suggestion of withdrawal symptoms. One of these was slightly uneasy for 48 hours after the drug was withdrawn and the temperature of another one was a fraction of a degree lower than normal for 4 days. The other three exhibited no symptoms of distress or depression.

The picture shows that Professor Abe's monkey became ill after the codeine was withdrawn, but the delay of vomiting until the fourth day and the apparent complete recovery on the sixth day suggests that some other factor than withdrawal of the codeine may have been responsible in part for the illness. Data on other codeine-addicted animals would show whether this one had the expected sequence of symptoms, but this is the only monkey I know of for which a measurable degree of codeine addiction is claimed. My morphine-addicted animals became very ill during the first 24 hours after the drug was discontinued, and their temperatures, which were markedly depressed, did not return to normal for 14 to 20 days, but these animals were much more seriously addicted than the one shown by Professor Abe.

Himmelsbach, Gerlach, and Stanton (*37*), using measurable abstinence hyperirritability as their criterion of addiction, demonstrated the development of tolerance and physical dependence to codeine by the rat.

Discussion

This review of the clinical and animal experimental literature shows that, while codeine addiction is certainly not a myth, and in some cases the withdrawal signs and symptoms are as severe as those which follow withdrawal of morphine from morphine addicts, codeine is less addictive than morphine.

While codeine would seem to have a peculiarly specific appeal to certain persons, the chief factors which lead to codeine addiction appear to be:

1. Its injudicious use in the practice of medicine.
2. Inadequate legal control.
3. Difficulty in obtaining the usual addiction drugs.

The chief factors which operate to prevent greater incidence of codeine addiction appear to be:

1. Its euphoric effects are of decidedly lower order than either morphine or heroin.
2. The cost of addiction-sustaining amounts of codeine is much greater than for equally effective doses of morphine or heroin.
3. Its low solubility (4 percent) and necessarily larger dose makes the bulk of an effective addiction dose decidedly inconvenient to administer; for example, 5 grains (0.325 gm.) of codeine would require more than 8 ml. of distilled water, whereas 1 grain of morphine can be dissolved easily in 1.25 ml. of distilled water.

Codeine is certainly liable to cause addiction when used in excessive amounts, or when it is administered to persons whose unstable nervous make-up causes them to become easy victims of the seductive calm produced by opiates.

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PART II. STUDIES OF PHYSICAL DEPENDENCE ON CODEINE

By C. K. HIMMELSBACH, *Passed Assistant Surgeon*, and HOWARD L. ANDREWS, *Associate Physicist, United States Public Health Service.* With the coopera- tion of WARD WORKMAN, *Head Guard Attendant, United States Public Health Service, United States Public Health Service Hospital, Lexington, Ky.*

Studies of the addiction properties of certain morphine derivatives, which were started at the United States Penitentiary Annex, Fort Leavenworth, Kans., in 1933, have been continued at the United States Public Health Service Hospital at Lexington, Ky., as a phase of the cooperative effort of a number of organizations [1] to find a nonaddictive substitute for morphine (*1*). This approach to a pos- sible solution of the problem of drug addiction is based on the hypothesis that variations in chemical structure often cause variations in physiological effects, and that if the effects can be identified with certain portions of the morphine molecule it might be possible to suppress or eliminate undesirable actions and at the same time retain or improve the desirable effects.

This phase of the cooperative investigation concerns the detection and measurement of differences in addiction effects of certain mor- phine derivatives and the correlation of these differences with altera- tions in chemical structure.

The fact that codeine is an addictive drug of definitely lower order than morphine causes it to rank in importance next to morphine as a standard by which new substances may be more accurately evaluated in regard to their addiction liabilities.

In a previous study (*2*) codeine was substituted for the morphine being administered to seven strongly addicted patients by replacing, on successive days, one of the subcutaneous doses of morphine by a subcutaneous dose of codeine so that from the fourth day until withdrawal only codeine was given. The doses of codeine were adjusted in each case to the minimal amounts necessary to prevent abstinence signs and symptoms. After 8 to 14 days of continuous administration codeine was abruptly and completely withheld. The mean abstinence syndrome which occurred was about equal in severity, but seemed to be slower in onset than that exhibited by patients undergoing morphine withdrawal. Since that time the

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[1] The organizations taking part are the Rockefeller Foundation, the National Research Council, the U. S. Public Health Service, the U. S. Bureau of Narcotics, the University of Virginia, and the University of Michigan.

methods for studying addiction characteristics of substituted drugs have been refined and expanded; hence, it seemed advisable to repeat the study and to obtain more complete data on the duration of addiction action of codeine and its comparative addiction potency. Such a study should not only result in a clearer appreciation of the relationship of the addiction propensities of codeine and morphine, but should provide a second standard for estimating addiction liabilities of new morphine derivatives or substitutes.

General Considerations

Addiction to an opiate embraces three intimately related phenomena: Physical dependence, psychical dependence (habituation), and tolerance. The studies reported in this section chiefly concern physical dependence.

The only recognized criterion of physical dependence is the appearance of the characteristic abstinence syndrome following withdrawal of all addictive drugs being administered to the addicted patient. When a drug of questioned or unknown addiction properties is completely substituted for the morphine being administered to an addict, and the appearance of the abstinence syndrome is deferred until the substance is withheld, that drug is considered to possess definite addiction liability.

The next consideration is, how does the addiction liability of this drug compare with that of morphine? The methods which are being developed to answer this question, although not complete, are based on the theory that an action of a drug is, in effect, two-dimensional, the components of action being *intensity* and *duration*. The total effect of drug action might be estimated from the included area of a graph plotted from measurements of these components. If this be true, it would seem reasonable to expect that when the duration and intensity components of physical dependence action can be measured, it should be possible to compare quantitatively this addiction effect of one compound with that of another.

However, there is some question as to whether or not a comparison of only the physical dependence effects of two drugs would give a true picture of the relationship of their respective addiction liabilities. We are of the opinion that comparisons of the relationships of both the physical dependence and analgetic actions of narcotic drugs would be significant, for a safer drug than morphine from the standpoint of addiction must be one in which the total physical dependence effect has been greatly reduced; but to be of clinical value its total analgetic action must be fully retained or increased. Narcotic drugs are administered chiefly to obtain relief from pain; the development of addiction is an undesirable side action.

This concept is illustrated diagrammatically in figure 1.

If curve A represents the analgetic and curve B the addictive effect of a hypothetical compound, the repeated administration of such a
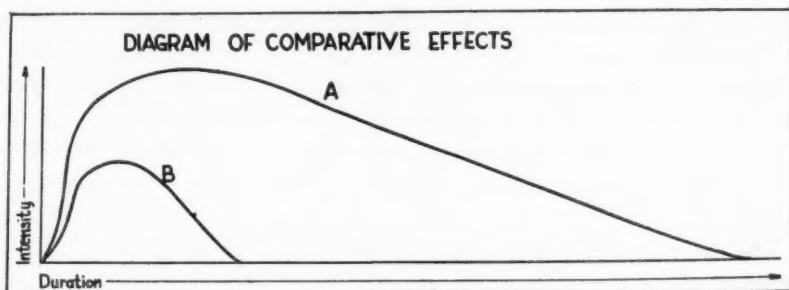

DIAGRAM OF COMPARATIVE EFFECTS

FIGURE 1.

drug for the clinical control of pain should be much safer from the standpoint of addiction than if these relationships were reversed. The converse, that is, A representing addiction effect, and B representing analgesia, is probably somewhat characteristic of morphine.

Thus, it would seem that the results of these substitution studies of physical dependence must be considered in relation to the concomitant changes which take place in the analgetic actions of the drugs being investigated (4).

Methods

The intensity of the abstinence syndrome may be scored with a fair degree of accuracy at any time during the course of studying addicts under controlled conditions (3) by using the system of recording and scoring abstinence phenomena shown in table 1.

TABLE 1.—*Point system for measuring abstinence syndrome intensity by the day (D) or by the hour (H)*

Signs	By day (D)		By hour (H)	
	Points	Limit	Points	Limit
Yawning	1	1	1	1
Lacrimation	1	1	1	1
Rhinorrhea	1	1	1	1
Perspiration	1	1	1	1
Mydriasis	3	3	3	3
Tremor	3	3	3	3
Gooseflesh	3	3	3	3
Anorexia (40 percent decrease in caloric intake)	3	3		
Restlessness	5	5	5	5
Emesis (each spell)	5		5	5
Fever (for each 0.1° C. rise over mean addiction level)	1		1	10
Hyperpnoea (for each resp./min. rise over mean addiction level)	1		1	10
Rise in a.m. systolic B. P. (for each 2 mm. Hg over mean addiction level)	1	15	1	10
Weight loss (a. m.) (for each 1b. from last day of addiction)	1			

Total abstinence syndrome intensity per day or per hour is the sum of the points scored in the (D) or (H) columns, respectively, with due attention to the limits.

Through the use of this system it is possible to depict the onset, development, and decline of the abstinence syndrome. The duration of physical dependence action of a drug is estimated by scoring the abstinence syndrome at hourly or shorter intervals after withdrawal until its maximum intensity has been passed. The mean values for a group are plotted on a graph with intensity points as ordinates and hours as abscissae. The time at which the abstinence syndrome reaches 50 percent of its maximum intensity is considered to represent a reasonably accurate expression of the duration of action of the drug in question, for by that time the drug's addiction effect appears to be insignificant (4).

The intensity or potency of physical dependence action of a drug under study (in relation to morphine) is estimated from the relationship of the amounts of single doses which are equally effective in satisfying physical dependence. For the sake of uniformity the amounts are corrected to an arbitrary standard of 50 mg. of morphine sulfate. Since potency varies inversely with the dose, the results are expressed as their respective reciprocals. For example, if 5 mg. of drug X is as effective as 25 mg. of morphine, the potency of X would be expressed as $\frac{1}{10}$, that of morphine being $\frac{1}{50}$ (4).

Such observations were made on 19 patients who were still actively addicted when admitted to this hospital. In each case opiates were withheld until objective abstinence phenomena became sufficiently intense to establish the presence of valid physical dependence. The patients were then physiologically stabilized on morphine sulfate. This drug was administered in the minimal amounts necessary to prevent the appearance of abstinence phenomena. Four doses each day were administered subcutaneously in the subscapular region.

In one group of 16 patients, after 7 to 10 days on morphine, codeine hydrochloride was abruptly and completely substituted. In this group the codeine was administered subcutaneously in the respective minimal amounts required to match, as nearly as possible, the state of physiological equilibrium obtained with morphine. While most of the patients in this group were given 4 daily injections, in some it was possible to maintain equivalent comfort with the same amount of codeine divided into 3 doses.

Since Wolff (5) has recently suggested that codeine given by mouth is less addictive than that administered parenterally, it seemed desirable to study this question. Accordingly, in a second group of 3 patients, after preliminary stabilization on morphine administered first hypodermically, then orally, codeine was given orally for 10 days. In this group the drugs, in powder form, were incorporated into capsules of a uniform size, and these were given 7 to 10 times daily. Although the number of capsules per dose and the number of administrations per

day varied with each patient, these factors were kept constant for each individual on both morphine and codeine. The doses were adjusted by changing the amounts contained in the capsules in order to keep the number constant. To get a smooth effect and to prevent gastric disturbance, it was found necessary to give a larger number of smaller doses instead of a few large doses.

In both groups withdrawal of codeine was abrupt and complete after 10 days of continuous administration. Observations for abstinence phenomena were made three times daily during the course of drug administration, and more frequently after withdrawal and during the transition periods.

Results

The results on the first group of 16 patients are shown in figure 2, in terms of mean daily abstinence syndrome intensity for the last 7 days of morphine stabilization, the entire period of codeine substitution, and following abrupt withdrawal of codeine. It will be noticed that the abrupt substitution of codeine for morphine was followed by the appearance of the abstinence syndrome to an intensity of 17 points on the second day, and that its intensity gradually subsided thereafter while codeine was being administered but did not quite regain the morphine stabilization level. Following withdrawal of codeine the abstinence syndrome reappeared and reached its high level of 34 points intensity on the second day. When compared directly with the mean abstinence syndrome of 65 controls undergoing morphine withdrawal, it will be seen (fig. 2) that the codeine syndrome is the less severe.
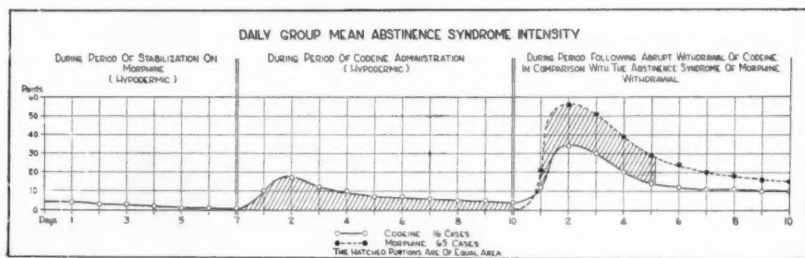
FIGURE 2.

Since it seemed likely that this difference in the abstinence syndromes of morphine and codeine indicated a partial loss of physical dependence during codeine administration, an attempt was made to measure this loss and compare it with the difference in the abstinence syndromes. The area (hatched in fig. 2), bounded by the base line and the abstinence syndrome intensity curve during the period of codeine administration, is considered to be roughly representative

of the mean total loss of physical dependence during that period. When this area was compared with the area of the difference between the mean abstinence syndromes of morphine and codeine, it was found that the difference for the first 5 days of withdrawal might be accounted for on the basis of equivalency. This equivalent area of the difference is also hatched in figure 2.

A further comparison of these patients during the periods of morphine and codeine administration is given in table 2. This table gives the mean values for temperature, respiration, blood pressure, and caloric intake during the last 7 days on each of the drugs, and also shows the average weights on the last days of codeine and morphine administration and the average daily dosages of the two drugs.

In the main, insofar as these measures of physiological equilibrium are concerned, the satisfaction of morphine addiction by codeine was rather complete. It will be noticed that the mean systolic blood pressure during codeine substitution was increased 6 mm. over the morphine level; however, an analysis of this difference showed it to be statistically insignificant. The mean caloric intake was 130 calories per day less on codeine than on morphine, but this difference of −4 percent was also found to be statistically insignificant.

Assuming equivalent physiological stabilization on the two drugs, the data on dosage would indicate that the potency of codeine HCl is $\frac{1}{259}$, indicating that 259 mg. of codeine HCl possesses addiction potency equivalent to 50 mg. of morphine sulfate. Thus codeine HCl is but 19.3 percent as effective as morphine sulfate in the support of addiction. When only the alkaloidal bases are considered, this figure becomes 18.1 percent.

TABLE 2.—*Comparisons of several measures of physiological equilibrium during stabilization on morphine and after substitution of codeine*

	First group		Second group		
	(16 cases) M(s) to C(s)		(3 cases) M(s) to M(o) to C(o)		
Temperature, rectal,°C	37. 1	37. 1	37. 0	37. 0	37. 0
Respiration rate/min	16	17	15	16	16
A. M. systolic B. P. (mm. Hg)	110	116	112	116	114
Caloric intake, daily	2,810	2,680	2,660	2,530	2,700
A. M. weight (last day), kg	64. 81	64. 46	66. 34	66. 07	66. 45
Total daily dose (mg.)	158. 7	822. 5	160	200	825

M=morphine sulfate; C=codeine HCl; (s)=subcutaneous administration; (o)=oral administration.
Except for weight the values in columns other than "M(o)" are group mean values for the last 7 days on morphine or codeine; the values in the "M(o)" column are the group means for 4 days.

The duration of physical dependence action of codeine, estimated in the manner described under "Methods," was found to be 16.2 hours. It will be noted in figure 3 that at this time the codeine

abstinence syndrome had reached 50 percent of its maximal intensity. The value for morphine, also shown in figure 3, is 14.4 hours.

ONSETS OF ABSTINENCE SYNDROMES FOLLOWING ABRUPT WITHDRAWAL OF HYPODERMIC AND ORAL CODEINE IN COMPARISON WITH ABRUPT WITHDRAWAL OF MORPHINE
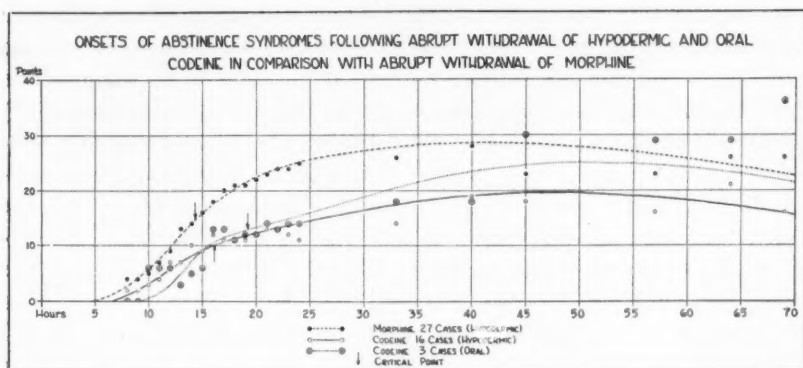
FIGURE 3.

In the second group of 3 patients to whom codeine was administered orally after preliminary stabilization on morphine given first subcutaneously then orally, it was found that a 25-percent increase in dose was required when the shift was made from parenteral to oral administration of morphine (table 2). However, the amount of codeine was about the same in both groups. The results of this study, presented in figure 4, show the daily mean abstinence syndrome intensities for the successive periods: Subcutaneous morphine, oral morphine, oral codeine, and withdrawal. In this figure the mean withdrawal curves for subcutaneous morphine and codeine are shown for purposes of comparison.

DAILY GROUP MEAN ABSTINENCE SYNDROME INTENSITY
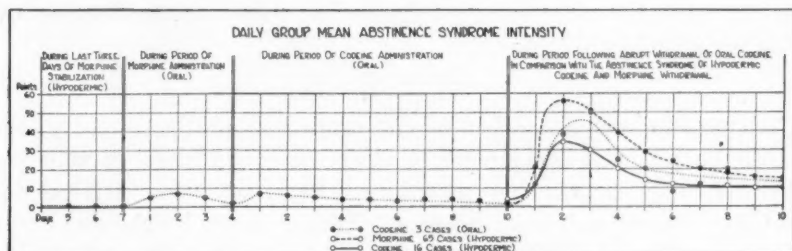
FIGURE 4.

The transition from oral morphine to codeine was much less eventful than in the first group. Satisfaction of physical dependence by codeine administered *per os* appeared to be slightly better than by the parenteral route (table 2 and fig. 4). The abstinence syndrome which appeared following the last dose of codeine was slower in onset than that of either morphine or codeine administered subcutaneously (fig. 3), and of greater intensity than the first group (fig. 4).

Discussion

A true comparison of the results of this study with the one previously reported (*2*) is not possible because the data of the former group are not sufficiently complete to be scored by the present system of abstinence syndrome intensity evaluation. However, an analysis by the degree method of abstinence syndrome intensity evaluation (*3*) indicates that the mean abstinence curve of the former codeine substitution group more closely approximates that of the morphine controls than does the present group. This discrepancy might be due to either or both of the following outstanding differences: 1. Substitution of codeine was accomplished gradually over a period of 4 days in the former group (*2*), but abruptly in the present group. As a result, less loss of physical dependence intensity may have occurred in the former group. 2. The mean daily codeine requirement of the first group was 1.74 gm. (*2*), whereas that of the present group was 0.822 gm. The above comments refer only to codeine administered subcutaneously.

The matter of incomplete cross-tolerance between morphine and codeine, although of no serious consequence, is thought to be of sufficient interest to mention the fact that definite flushing of the skin of the head and hands following the first few doses of codeine was again observed in some cases. Tolerance to this developed within 2 to 3 days in all cases.

Although 3 cases constitute a small group from which to draw conclusions, our only purpose in administering codeine by mouth was to learn whether or not this drug given in this manner would satisfy and support pre-established physical dependence. It is obvious that it does and that the abstinence syndrome is no less intense because of administration by this route.

Summary

Codeine administered either subcutaneously or orally supports pre-established physical dependence to morphine when given in amounts about 5.2 times greater than morphine. Satisfaction of physical dependence by codeine is not complete. This is shown by the consistent appearance of mild abstinence phenomena during the course of codeine administration, and by the less severe abstinence syndrome which occurs following withdrawal of codeine. This difference in intensity of the abstinence syndromes of codeine and morphine withdrawal would appear to be due in part to the loss of physical dependence which occurred chiefly in the transition period.

The duration of the physical dependence action of codeine was estimated to be 16.2 hours, which is not significantly greater than that of morphine. The comparative intensities of the physical dependence effects of codeine and morphine are $\frac{1}{259}$ and $\frac{1}{50}$, respectively.

References

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(*4*) Himmelsbach, C. K.: Studies of certain addiction characteristics of (a) dihydromorphine ("paramorphan"), (b) dihydrodesoxymorphine-D ("desomorphine"), (c) dihydrodesoxycodeine-D ("desocodeine"), and (d) methyldihydromorphinone. J. Pharm. and Exp. Therap., **67**: 239 (1939).

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PART III. EFFECTS OF CODEINE ON THE ELECTRICAL POTENTIALS OF THE CEREBRAL CORTEX

By Howard L. Andrews, *Associate Physicist, United States Public Health Service.* With the cooperation of Ward Workman, *Head Guard Attendant, United States Public Health Service, United States Public Health Service Hospital, Lexington, Ky.*

The psychological effects of single doses of, and addiction to, the opiates have been recognized for many years. It seemed desirable to investigate this apparent central nervous system action by means of electroencephalography, which gives a direct measure of the electrical activity of the cerebral cortex.

It has been well established that the electrical potentials recorded from electrodes placed on the scalp surface originate from the cerebral cortex (*1, 2*). These records may contain some artefacts of extracranial origin, but in general these can be distinguished from the cortical potentials.

Brain potential studies were carried out on 7 of the group of patients who were stabilized on morphine, substituted on codeine, and withdrawn from the latter drug. The rest of the group was excluded because of possible central nervous system pathology. In no case was the pathology sufficient to interfere with the physiological studies, but it was deemed wise to use only the best available cases for the brain potential study.

It is recognized that the number of cases is small, but the consistency of the results indicates that only minor differences would be found in a larger group.

Methods

Since the apparatus and methods used in electroencephalography are not yet standardized, the recording apparatus used in the present experiments is briefly described.

A four-channel amplifier-oscillograph system was used. The resistance-capacitance coupled amplifiers were push-pull, modified to eliminate interference between channels and to maintain balance between the two sides of each amplifier. The frequency response was uniform from 5,000 cycles to 0.5 cycle when no filters were used. All of the records described here were taken with a low-pass filter in the circuit. This greatly reduced the amplitude of all frequencies above 200 cycles but did not appreciably alter the amplification of the low

20

frequency band where most of the prominent cortical frequencies are found. The four amplifiers were carefully matched, both in frequency response and sensitivity.

. Each amplifier was connected to one galvanometer of a Westinghouse type PA oscillograph. These galvanometers have a uniform response to all frequencies up to about 1,500 cycles and are critically damped to prevent overshooting. A fifth galvanometer provides a continuous time line and a means of recording signals on the film. The records were photographed on Eastman No. 809 bromide paper moving at the rate of 35 mm. per second.

Two types of head electrodes were used. During addiction, when the patients were comfortable, chlorided silver "hats" (*3*) were cemented with collodion to the head surface after cutting the hair. During withdrawal, however, the time required to place and remove a set of these electrodes proved so annoying to the patients that a new type of suction cup electrode was devised (*4*). These permitted rapid application and removal, and eliminated the need for the disagreeable ether-alcohol mixture used to remove the collodion-cemented type of electrodes. There was no detectable difference between records taken from the two types of electrodes.

All records were taken with the patient reclining with eyes closed in a darkened, electrically and acoustically shielded room. An observer in the room with the patient signalled movements or any other disturbance which might introduce artefacts. All recording apparatus was in an adjoining room so that the patient was undisturbed by the experimental procedures. An attempt was made to have the patient in the same state of mental relaxation each time a record was taken. This was not always possible, since the substitution of codeine for morphine sometimes produced changes in personality and emotional state (see **Part IV**).

When a patient had been stabilized on morphine for several days, a record was taken at the time when he would normally receive a regular injection. At this time (11:00 a. m.) 5 hours had elapsed since the preceding dose. Immediately following the record his stabilizing injection was given and a second record was taken 45 minutes later. At this time the effect of the dose was presumably maximal. After not less than 7 days of codeine substitution this procedure was repeated. At this time stabilization on the codeine was practically complete (Part II, fig. 2).

An attempt was made to take records throughout the period of withdrawal at 12, 24, and 36 hours of abstinence, but for several reasons this schedule could not be maintained. In some cases palliative treatment had to be given, preventing further study during the withdrawal period.

Electrode Placements

Since previous workers had found important differences between the records taken from different head areas, it seemed highly desirable to record from restricted cortical areas. This can best be done by means of electrode pairs placed over the areas to be studied (*3*, *5*).

In this study the standard frontal, precentral, and occipital electrode placements of Jasper and Andrews (*3*) were used throughout. Homologous pairs were placed over each hemisphere. In addition to the bipolar records taken from these six pairs, monopolar records were taken, using one electrode on either ear connected together as a diffuse lead. During withdrawal, when the patient was resentful or irritable, the left frontal and left precentral pairs were omitted. It was then possible to obtain both bipolar and monopolar records on two films instead of the customary four.

When electrodes were first applied, the positions were carefully marked on the scalp and sufficient hair clipped to permit good electrode contact. These spots were kept clipped throughout the course of the experiment so that identical electrode placements were obtained for every run.

Results

The records were carefully studied to determine the most commonly observed frequencies, the percentage of time these frequencies were present, the presence of the slow waves found in certain pathological states, amplitude, regularity, and any other characteristics that seemed pertinent.

The percentage activity was measured on one meter of film which had been carefully selected as being representative of the activity. Only waves having an amplitude of 5 microvolts or more were considered as representative of cortical activity. Frequency measurements were always made in groups of three waves, the assigned frequency being the mean of 30 measurements.

The alpha waves (8 to 16 per second) were the most prominent features of all the records. Some activity of beta frequency (17 to 30 per second) was seen from the precentral region, but this occurred only in scattered bursts from some individuals. The amount of beta activity did not change significantly during the course of the experiments.

Occasional groups of waves of abnormally long duration were found in many of the records, particularly those taken during withdrawal. Although some of these could not be correlated with eye blinks or other gross movements, their infrequent appearance suggests that they are artefacts and do not represent pathological cortical activity.

The percentages of precentral and frontal alpha were in general less than the occipital alpha percentage that would be expected from the work of Rubin (6) with normal persons.

No particular mention will be made here of the precentral and frontal records, since there were no significant changes in these which were not found in the occipital records.

The alpha rhythm.—During morphine addiction the 7 subjects formed a homogeneous group as far as the occipital alpha rhythm is concerned. In every individual the percentage of occipital alpha activity, measured from either bipolar or monopolar leads, was between 60 and 90 percent. This is in accord with unpublished findings on a larger number of men who have been studied during morphine addiction. During stabilization the alpha activity was uniformly high and the percentage distribution was quite different from that found by Davis and Davis (7) for normal persons. Because of the homogeneity of the group, and because each individual followed practically the same course throughout the study, the results are given in terms of the averages for the group.

The percentage of the alpha activity is invariably increased by the administration of the stabilizing dose. During codeine stabilization the percentage activity in the bipolar records was lower than in the corresponding records taken during morphine stabilization. In spite of the fact that the stabilizing codeine dose produced a greater increase in alpha percentage than the corresponding morphine dose, the level of activity during codeine administration was lower than that during morphine administration. In the bipolar records the percentage *following* a codeine dose was less than the percentage *before* the morphine injection. This is illustrated in figure 1.

During codeine administration there was a wider divergence between the activities of the two hemispheres. This particular group always showed a greater activity from the right hemisphere, both with monopolar and bipolar leads. This was checked by reversing amplifiers on several occasions, but the higher percentage continued to be recorded from the right hemisphere. Considering the bipolar leads, figure 1 shows a bilateral difference of 2 percent before the morphine injection and 11 percent before the codeine injection. The monopolar leads show only a very slight increase in the bilateral difference following substitution.

The mean alpha frequencies from the occipital leads reflect quite accurately the changes in alpha percentage (fig. 2.) The effect of the stabilizing dose, whether of morphine or codeine, was to decrease the alpha frequency. Following the substitution of codeine, the alpha frequency increased to such an extent that the frequency

after the codeine dose was higher than the frequency *before* the morphine dose.

The substitution of codeine also results in greater differences between the frequencies of the two hemispheres. These frequency differences are consistent with the percentage findings, the right hemisphere having the greater alpha percentage and the lower alpha frequency.

EFFECTS OF CODEINE SUBSTITUTION ON THE OCCIPITAL ALPHA PERCENTAGE

MEAN OF 7 CASES

- Right Occipital Monopolar
- Right Occipital Bipolar
- Left Occipital Monopolar
- Left Occipital Bipolar

MORPHINE STABILIZATION — TRANSITION — CODEINE SUBSTITUTION

BEFORE INJECTION — AFTER INJECTION — BEFORE INJECTION — AFTER INJECTION
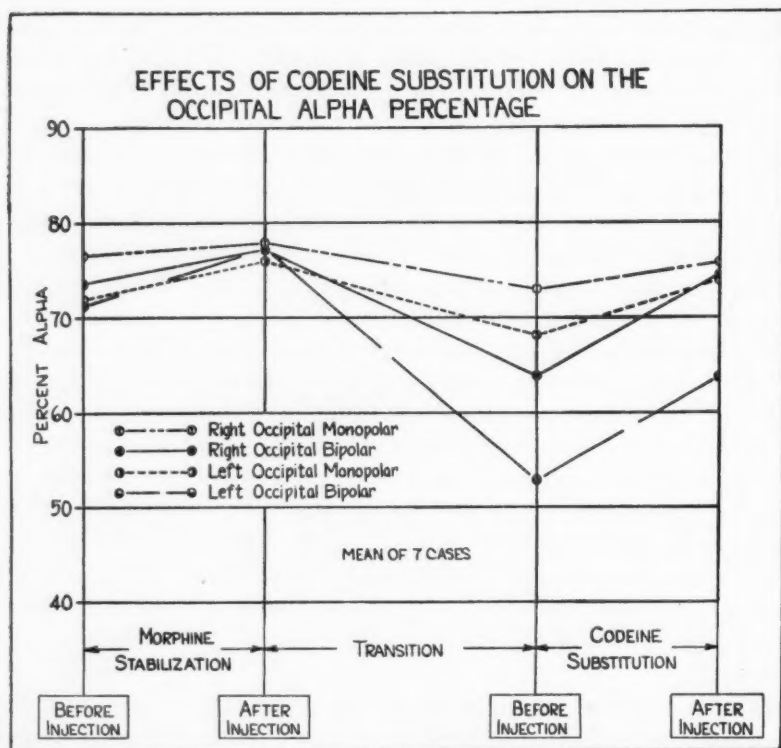
FIGURE 1.—Average occipital alpha percentages during morphine stabilization and codeine substitution. The bipolar leads show an increased bilateral asynchronism during codeine substitution.

There was nothing abnormal about the amplitude of the alpha rhythm, and this did not change significantly through the course of the study. The occipital bipolar alpha potentials varied from 20 to 50 microvolts, while the monopolar occipital alpha potentials ranged from 60 to 110 microvolts.

Withdrawal.—It is rather difficult to obtain records when the patients are in the active stage of withdrawal from the drug. In the present group of cases a complete series of withdrawal records was obtained from only one man. The occipital alpha percentage for this patient, plotted throughout the course of study, is shown

in figure 3, with the abstinence intensity syndrome points plotted during the withdrawal period. Figure 4 shows samples of the actual records taken on this case. The most striking feature of figure 3 is the high alpha output during withdrawal when the patient was irritable, restless, nauseated, and very resentful of the experimental procedure. In all the records taken during withdrawal there were many sections which had to be ruled out because of movements. Although the one case shown in figure 3 represents the only example of a complete record throughout withdrawal from
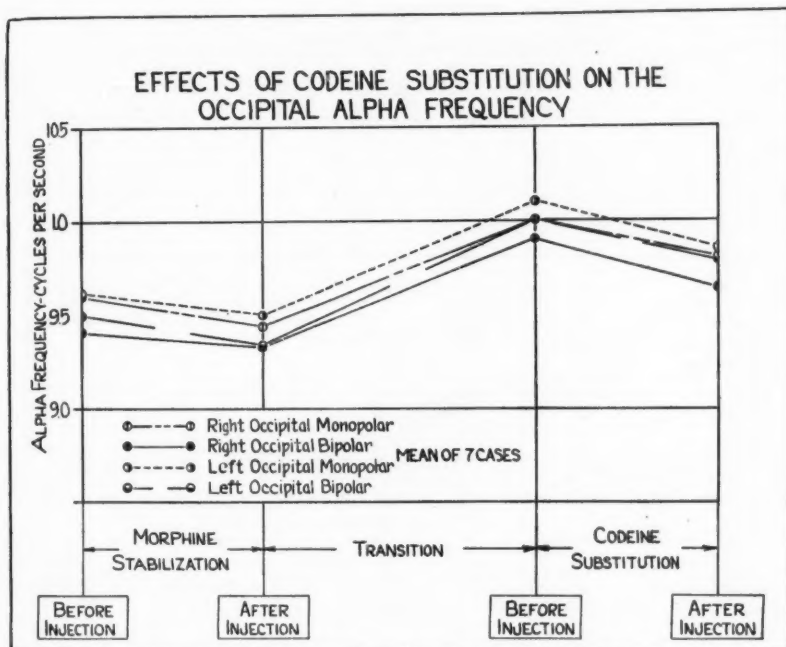

FIGURE 2.—Average occipital alpha frequencies.

codeine, enough scattered records on other cases are available to justify the statement that during the active phase of withdrawal the alpha output is at least as great, both in percentage and amplitude, as during addiction. In this respect there is little difference between withdrawal from morphine and withdrawal from codeine.

Single Dose Experiments

Records were taken on two cases to determine the effects of single doses of codeine. Both had been previously addicted to morphine or heroin, but had received no narcotics [1] for at least 11 months. Both

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[1] One of these men had received a single dose of morphine 6 weeks before the present study, but it is believed that this had no appreciable effect on the results reported here.

men were thoroughly familiar with the experimental procedure and showed no concern or apprehension. Records were taken before the injection and at hourly intervals following injection until the sub-jective drug effects had completely disappeared. In these cases light stimuli of 1 to 3 seconds duration from a fairly bright source (50 candlepower automobile headlight bulb with condensing and projec-tion lenses) were used. In addition to the regular film measure-ments, alpha blocking times (8) were calculated.
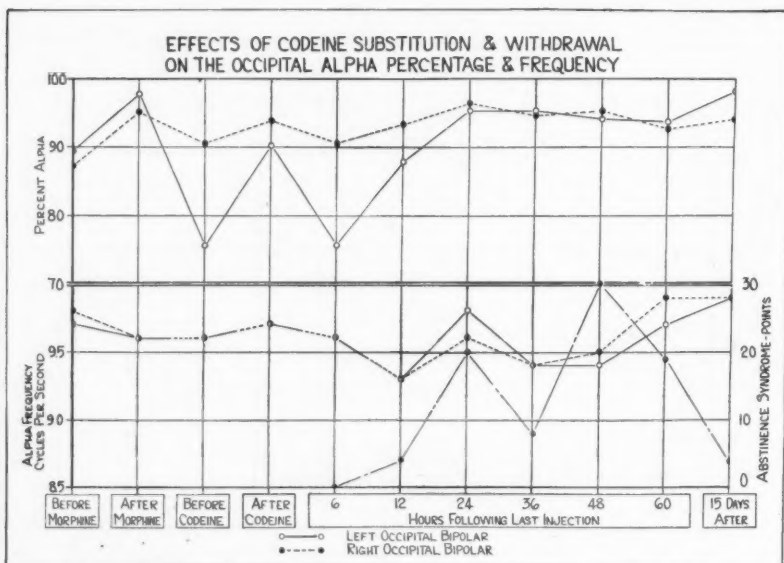

FIGURE 3.—Occipital alpha frequencies and percentages during stabilization, substitution, and withdrawal (1 case). The high alpha percentage is maintained during withdrawal. The abstinence syndrome points show the course of the withdrawal.

One of these cases was a "dominant" alpha subject (7) showing before injection at least 90 percent alpha activity from all occipital leads. There was no significant change in alpha percentage, fre-quency, amplitude, or grouping in any of the records taken after the subcutaneous injection of 110 mg. of codeine hydrochloride (fig. 5). The only significant change found following injection was an increase in the alpha blocking times as shown in table 1.

TABLE 1.—*Alpha blocking times, monopolar occipital leads. Case No. 1*

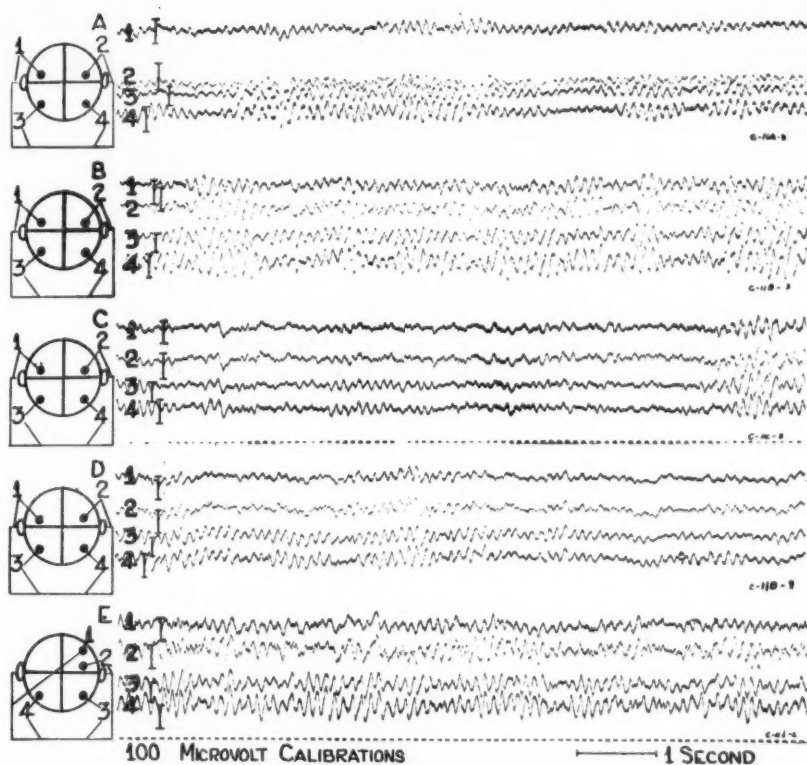|	Number of stimuli	Mean blocking time (sec.)	Standard deviation
Before injection	9	0.233	0.029
1 hour after	10	0.388	0.028
2 hours after	10	0.289	0.041
3 hours after	6	0.262	0.042

100 MICROVOLT CALIBRATIONS   1 SECOND

FIGURE 4.—Samples of records taken during stabilization, substitution, and withdrawal.
A. During stabilization, 5 hours after the preceding injection.
B. One hour later following the injection of 45 mg. of morphine.
C. On the seventh day of codeine substitution, 8 hours after the preceding injection.
D. One hour later, following the injection of 315 mg. of codeine.
E. Sixty hours following the last codeine injection. At this time the patient was showing 19 points of abstinence.
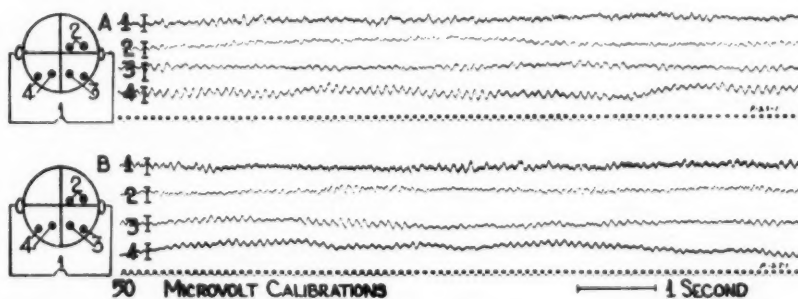

50 MICROVOLT CALIBRATIONS   1 SECOND

FIGURE 5.—The effect of a single dose of 110 mg. of codeine in an addict who had received no drugs for 1 year.
A. Before injection.
B. One hour following injection. There is no important difference between the two records.

The difference between the preinjection blocking time and that found 1 hour after injection appears to be significant. The critical ratio of these means is 5.5. The differences between the other blocking times are not statistically significant.

A similar experiment performed on the same individual 6 weeks previous to the one described above, in which 20 mg. of morphine sulfate were administered instead of the codeine, gave comparable results.

Case 2 had a low alpha output in all occipital leads and was definitely in the "rare" classification of Davis and Davis (7). The alpha output was so low that good light blocks could not be obtained. The subcutaneous injection of 175 mg. of codeine hydrochloride did not significantly change the alpha output in any way. In figure 6 records before and after injection are compared with a similar record taken 12 months previously while the subject was addicted to, and stabilized on, morphine.

100 MICROVOLT CALIBRATIONS   ⊢────── 1 SECOND
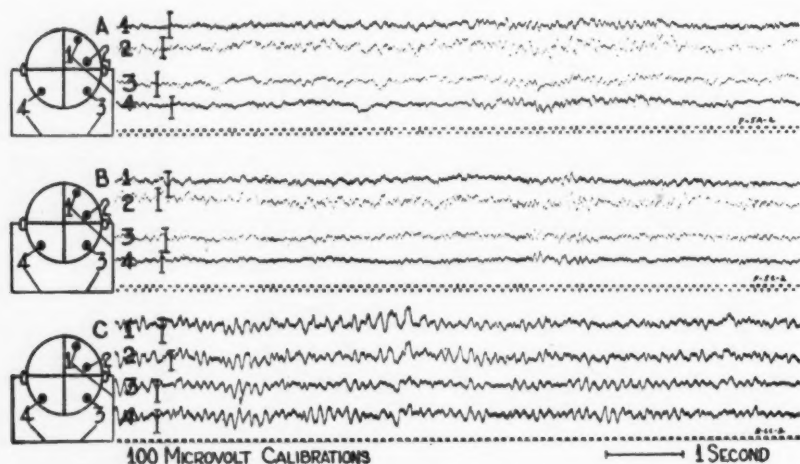
FIGURE 6.—The effect of a single dose of 175 mg. of codeine in an addict who has received no drugs for 11 months.
A. Before injection.
B. One hour after injection.
C. Eleven months prior to the above records when the patient was addicted to and stabilized on morphine.
There is no significant difference between A and B but C shows the increased alpha activity found during maintained addiction.

Occasional waves of abnormally long duration (150 to 220 ms.) can be seen in the records of figure 6. This case gave no history of any illness suggestive of central nervous system pathology which might explain the slow waves.

Discussion

Although the number of cases is rather small, the results from each member of the group are in good agreement and it is believed that certain conclusions can be drawn.

During stabilization on morphine the percentage of alpha activity found in the occipital leads is definitely greater than would be anticipated from a group of normal individuals (7). This statement could not be made from the results on the seven cases discussed here, but studies of a larger number of men indicate that during addiction practically all cases fall into the "dominant" group, with a smaller number in the "subdominant" and "mixed" groups. This fact, together with the fact that a single injection of either morphine or codeine produces little change in the alpha activity (in individuals who have been addicted but who have received no drugs for 1 year), suggests that the high alpha output found during addiction is in some way related to the addiction, and is not an acute drug effect.

If the above hypothesis is true, it would appear that addiction after codeine substitution is less intense than that during the preceding morphine stabilization. This suggestion is strengthened by the fact that the intensity of the abstinence syndrome following codeine substitution is less than the intensity following direct withdrawal from morphine.

Although a high percentage of occipital alpha activity is found during addiction and during the acute withdrawal period, this high percentage is not necessarily maintained during the period of convalescence following the active phase of withdrawal. In some patients the alpha output 2 or 3 months after abrupt withdrawal is definitely lower than that found during addiction and withdrawal.

The increased average alpha rhythm found during addiction is probably a factor of considerable importance since it is practically the only measure in which a decided difference has been found between the addiction and the post-addiction states. Even this measure breaks down in an individual case, for a given patient may maintain his high percentage alpha output following withdrawal.

The increased alpha output and the decreased alpha frequency produced by a stabilizing dose of either morphine or codeine during addiction indicates that the dose produces a cortical depression. This may not, however, be the direct result of the action of the drug on the cortex. Bremer (9) has shown (in cats) that the spontaneous cortical potentials increase in frequency as more afferent impulses reach the cortex. From the known actions of the opiates it seems most probable that the frequency decrease found after the injection is due to a

partial blocking of the afferent impulses. The higher frequency level observed during codeine stabilization would indicate that the blocking was less complete than during morphine administration.

An attempt was made to have the patient in the same psychological state of relaxation during each run. This was usually not possible because in general the patient was not psychically comfortable during the period of codeine administration. Whether the decreased alpha output found with codeine is due to this unrest or to the effect of the drug *per se* has not yet been determined.

There is no reason to believe that the action of codeine is such as always to reduce the alpha output from the left hemisphere more than that from the right. The results of the present study indicate only that the slight bilateral asymmetry which existed during morphine administration was accentuated by the substitution of codeine. The fact that there is a greater difference between the hemispheres during codeine administration suggests that the substitution of codeine alters the previously existing relations between the cortex and the lower centers.

The high alpha output during active withdrawal is rather surprising. It has been shown conclusively (*10*) that mental unrest tends to reduce the high alpha activity. Nevertheless, during withdrawal when mental unrest and physical discomfort are intense, the alpha percentage is at least as great as when the patients are stabilized on the drug. This increased activity is not specific for codeine withdrawal, for it has been observed many times following withdrawal from morphine and other opiates. Further work must be done before this phenomenon can be explained.

Summary

A consideration of the results described above leads to the following conclusions:

1. During addiction the percentage of occipital alpha rhythm is uniformly high.

2. The administration of the stabilizing injection of either morphine or codeine during addiction increases the alpha percentage and decreases the alpha frequency.

3. The percentage of occipital alpha activity is less during codeine stabilization than during morphine stabilization.

4. There are changes in alpha frequency corresponding to the changes in alpha percentage.

5. Bilateral asynchronism seems to be accentuated by the substitution of codeine for morphine.

6. During withdrawal from codeine, the occipital alpha percentage is usually at least as high as during addiction.

7. A single injection of codeine to a nonaddicted individual (but one who has previously been addicted) produces little change in the brain potentials.

8. A single injection does, however, increase the time required to block the occipital alpha rhythm.

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PART IV. EFFECT OF CODEINE ADDICTION ON BEHAVIOR

By ROBERT H. FELIX, *Passed Assistant Surgeon, United States Public Health Service, United States Public Health Service Hospital, Lexington, Ky.*

General Description

Observations of patients undergoing treatment for narcotic drug addiction will soon convince one that there is more to this phenomenon than tolerance and physical dependence. The changes in the patient as a whole go deeper than this and can be more fully understood when the personality is studied; in fact, the somatic phenomena must be attributed in part to emotional changes. The effect of emotion on blood pressure and respiratory rate, for example, have been described by Dunbar (*1*) and others.

Early in our studies it became apparent that physiological stabilization did not necessarily mean that the patients were receiving totally satisfying quantities of morphine. Two facts convinced us of this: (1) The daily dosage required to prevent the appearance of abstinence phenomena in our patients was almost without exception considerably less than that which had been used before admission; (2) while physical discomfort was avoided, emotional tranquillity, such as had been experienced in the outside world, was not achieved. This latter fact was forcibly brought to our attention when, in the course of stabilization, the minimum dosage was exceeded. These patients would, unless too thoroughly narcotized, be pleasant and amiable, but when the quantity of morphine was adjusted to our satisfaction, the complaint would frequently be heard that the dosage was too small, and there was an evident feeling of dissatisfaction.

The most probable explanation for this is a psychological one. These individuals are, in some phase of their existence, unsatisfactorily adjusted, and they feel that narcotics make for a happier total situation. This aspect of the etiology of morphine addiction in particular has been discussed at some length by Felix (*2*), and it is sufficient at this time to state that the addict, like his nonaddicted fellows, is, in the final analysis, attempting to obtain from life sufficient pleasure and satisfaction to live in psychic peace and comfort. He has found that some of the narcotic drugs will bring about this situation, albeit at a considerable price. The results seem to him worth the cost, and he returns to drugs again and again, even in the

face of inevitable imprisonment and social ostracism. As tolerance and dependence are built up, however, this psychic peace or relief from tension is not obtained with the original quantity of narcotics, and more must be taken to obtain the desired results. This increase is at least enough to take care of the psychic effect, and it is this *extra amount* which is missed when the patient is physiologically stabilized on our wards.

Since the psychiatric phase of habitual drug usage is of much importance, it must play a significant role in determining the addict's choice of narcotics.

In interviewing addicts and in reviewing their records, many were found to have used codeine for short periods of time, but this drug was in many cases discontinued as soon as a supply of some other opiate, particularly morphine or heroin, could be obtained. The reasons given were very rarely economic. Some said that they chose some other drug because of the low solubility of codeine in water, but even these admitted that the chief cause was the absence of "lift" or "kick" which was obtained from the other drugs. They stated that, while symptoms of abstinence would be forestalled, codeine in all other respects "left them cold." A few patients had relapsed to narcotics through using codeine, but these, too, had quickly returned to some other opiate. The great majority had used codeine in an attempt to satisfy their dependence when other narcotics were not available.

One patient (R. F.) stated: "I have used codeine by mouth and in the vein for as long as a week at a time and in amounts up to an ounce a week when I could not get morphine or heroin. The effect was something like morphine but not as strong. I do not like it as well as either morphine or heroin since I cannot get as much kick from it, even when I use very large doses." This man was an inadequate individual who would fall into the "psychopathic diathesis" class described by Kolb and Ossenfort (*3*), and by Felix (*2*). He found that drugs added something to his existence which made him more self-assured and comfortable.

A letter received from a former patient (F. L. M.) described his experience with codeine in the following amusing manner: "In 1932, I had about 200 one-half grain codeine tablets, but they wouldn't take my habit off.[1] Each time I would fix [2] it would swell my hands and lips; in fact it caused more misery than anything. I will say I used about 200 tablets in one day and night * * *. It would cause a headache * * *. So codeine is out in my books."

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[1] A drug addict's expression for relieving symptoms of withdrawal.

[2] A drug addict's expression for administering a hypodermic injection.

A particularly intelligent patient (C. L.) described an experience with codeine as follows: "At the time of the experience I am about to relate, I was using 3 grains of morphine intravenously 4 times a day. My supply of morphine becoming suddenly exhausted, and finding myself in a strange city, I was able after about 10 hours to obtain an ounce of codeine. The time that was spent in finding the source of supply from which I received this codeine caused moderate abstinence symptoms to appear because of the lack of my usual intravenous injection of morphine. I attempted to substitute this codeine for morphine. My first attempt to administer to myself an injection of this drug was a failure because of the low solubility of the stuff. I next tried taking it by mouth, and this route served, to a small degree, to relieve the withdrawal symptoms that were present, but not enough to produce a feeling of well-being. I continued to take codeine by mouth at about 20-minute intervals, the approximate amount taken at each dose was 15 grains, and the number of doses taken was 4. These 4 doses relieved the signs of abstinence to a certain degree, but never to the extent that morphine had been doing. Not being able to get the same feeling from this amount of codeine that I did from morphine, I continued to take about 15 grains at each dose for 6 more doses, ranging from 20 to 40 minutes apart (total number of doses, 10). (My method of taking this drug was to pour out in the palm of my hand an amount about the same as if I were taking a dose of bicarbonate of soda, this is why I say about 15 grains.) The final result was a sudden collapse on the street of a strange city approximately 2 hours after my last dose of codeine. The time of my collapse was in the late evening; I would judge about 6 o'clock. When I awoke the next morning at the hospital, I had a good bowel movement and felt all right. I was told by the nurse that the attending physician had given me a dose of calomel the night before. After eating a substantial breakfast I was discharged at my own request. When I put on my clothes I found that the remainder of the ounce of codeine was still in my pocket, so I took 2 more doses of about 8 grains each (by mouth), then threw the remainder away and continued to my destination, where I obtained a supply of morphine. After taking a slightly larger dose than usual, intravenously, I felt normal and continued to use morphine thereafter."

It is very significant that codeine was taken until narcotization was so great that the individual collapsed. Obviously the demands of physical dependence were far exceeded, and yet the man was not psychically satisfied. The euphoria of morphine, which was the will-o'-the-wisp he was pursuing, could not be captured. Emotional tranquillity could not be obtained. It is significant, too, that part

of the codeine was thrown away, and extremely so, that this was done *before* a supply of morphine was obtained. It takes but a short experience with addicts to learn how pitifully dependent upon narcotics they are, and how they live in constant fear of discontinuance of their source of supply. When, under these conditions, a quantity of narcotic drug which will forestall symptoms of abstinence is discarded, that drug must be very ineffective insofar as psychic satisfaction is concerned. This act takes on added importance when it is realized that this man was away from home where the appearance of abstinence phenomena might result in arrest.

If these cases are typical, one would expect to find a rather dissatisfied lot of patients when codeine is substituted for morphine, and such is the case. Every possible precaution was taken to keep the patients from knowing that a substitution had been made. From the time of admission all injections were made in the scapular region so that the back was always turned. The syringes were filled with the proper amount of medication and were then covered with a sterile towel before "shot time." They were not uncovered until the patient's back was turned. All injections were given in exactly the same way and the substitution date was a closely guarded secret. Within 12 to 18 hours after the substitution there was usually some evidence of narcotic deprivation, as was illustrated in figure 2, Part II, but the personality change was out of proportion to the physical symptoms. Irritability and mild depression were nearly constant findings for the first few days. Individuals who had formerly been cheerful and easy-going would be found to be rather short tempered and unhappy. They would take less interest in the state and care of their persons and rooms than they did while on morphine. They were not as talkative as they were while on morphine, particularly after they had been on codeine for several days. The degree of these personality changes would vary with the individual, but the direction of the changes was the same in all cases. The cooperation usually remained good, but in some cases this also suffered.

After the first 24 to 48 hours most physical evidence of narcotic deprivation disappeared, and from the physiological standpoint the patients were considered to be again stable. When closely studied, however, they were found not to be upon the same emotional level as formerly. They were vaguely unhappy and dissatisfied. They knew there had been some sort of a change in their medicine because they did not feel the same. The usual remarks were similar to those quoted above, that is, that they were not receiving a "kick" from their injections. One patient compared the change to eating cold potatoes; he was physically filled but not pleased or satisfied. The patients, while not unsociable, were certainly not gregarious. There

was a lessening of initiative amounting to lassitude, and while there was less complaining and irritability, there was also less spontaneous enthusiasm. Several patients stated that while they could not put it into words, they "just did not feel right." Fully half reported that they were more prone to dream, and then were not as rested on awakening. After a few days on codeine the majority expressed themselves as looking forward to the last injection, since what they were receiving was not sufficiently pleasant to be desirable.

The changes that occurred following abrupt withdrawal of codeine varied with the individual case and depended to some extent upon the severity of the physical symptoms of abstinence. The more ill the patient, the more irritable, depressed, disheveled, and unsociable he became. The changes were, of course, in the same direction as those that occurred at the time of codeine substitution, and in some cases were not much more severe. Soon after the patient knew that he would receive no more injections, he became mildly apprehensive on the basis of expecting an unpleasant experience. Some irritability frequently accompanied this apprehension.

Methods

It became more and more apparent as our investigations progressed that, in addition to a written account of the changes in emotion and behavior, some method of describing graphically what was observed would have very definite advantages. There are several reasons, which have been fully realized and considered, for hesitating to adopt a graphic method. The intent has not been to describe human behavior in terms of the variations of the slope of a line nor has it been forgotten that many aspects of behavior cannot be graphed as one would graph the fluctuations in temperature or pulse. It is also known that the descriptive terms employed for various grades of behavior or the categories used in these studies may not be identical with those which might have been selected by others. In spite of these objections it was felt that the employment of this method was very desirable in order that the psychiatric data could be compared to that of other phases of this study.

In order to reduce the possibility of error as much as possible, only those aspects of behavior were studied which could be observed fairly accurately by trained attendants, without the necessity of asking the patients leading questions. It was found that the information desired could be obtained by careful observation of the patients as they moved about the ward or lay in their beds. These aspects were divided into six general classes or categories: *Appearance, motor activity, mood, cooperation, speech* or oral productions, and *herd*, or the tendency to mingle and associate with one's fellows. Terms were

first selected which would describe each of these categories as they appear in the average normal individual. Thus we would say that such an individual, under normal conditions, would be clean and tidy in appearance, quiet with regard to motor activity, cheerful in mood, cooperative, conversational in speech, and gregarious. From this base line, terms were selected to describe four degrees or grades of the expanding and of the contracting personality. These were designated as 1, 2, 3, and 4 plus in the case of the expanding personality, and as 1, 2, 3, and 4 minus in the case of the contracting personality, with the higher numbers representing the more extreme degrees in both instances. Not only were the terms selected to indicate increasingly greater departures from normal in any category, but also so that the terms in the same grade in each category represented the same degree of departure from normal. The entire scale is reproduced in the following table:

Behavior rating scale

Score	I Appearance	II Motor activity	III Mood	IV Cooperation	V Speech	VI Herd
4+	Disrobes	Destructive	Hilarious	Unable to cooperate	Disconnected	Erotic
3+	Exhibition-istic	Dedifferen-tiated "push"	Ebullient	Ineffectual cooperation	Silly	Obnoxious
2+	Decorates	Hyperactive	Easily stim-ulated	Erratic co-operation	Garrulous	Affectionate
1+	Meticulous	Increased activity	Euphoric	Cooperates eagerly	Talkative	Hearty
0	Cleanly and tidy	Quiet	Cheerful	Cooperative	Conversa-tional	Gregarious
1—	Indifferent to appearance	Slow but restless	Unhappy, bored, gloomy	Perfunctory cooperation	Productions decreased	Companion-able
2—	Untidy	Procrasti-nates	Pessimistic, "blue"	Grudging cooperation	Does not ini-tiate conver-sation	Unsociable
3—	Disheveled	Responds slowly	Morose, de-pressed, weeping	Poorly co-operative	Monosylla-bic responses	Seclusive
4—	Uncleanly	Vegetates	Apathetic	Uncoopera-tive	Unrespon-sive	Withdrawn

It will be noted that in some instances two or more words have been employed to describe the same grade of a certain category. This has been done because it was found that sometimes one term did not describe all the phenomena of equal intensity which were to be observed. In these cases, if any one of the conditions could be observed, the patient received the corresponding score. Thus, a patient might be morose or weeping, or both, and in either instance would receive a score of 3 minus for mood.

Definitions

The terms used in this scale were defined for the guidance of the attendants as follows:

I. Appearance:

Disrobes.—Removes clothing at inappropriate times, exposing body.

Exhibitionistic.—Exposes genitals, or other parts of the body usually kept covered, wilfully and for the purpose of attracting attention, or, more broadly, behaving in such a manner as to attract attention.

Decorates.—Bedecks or adorns person with objects or trinkets which are not usually worn by patients in a hospital ward.

Meticulous.—Careful in trivial matters of dress or appearance. Finicky.

Cleanly and tidy.—Does not allow dirt to accumulate; cleanly about person; orderly and neat.

Indifferent to appearance.—Shows little regard or concern over condition of quarters or person.

Untidy.—Not neat in person or quarters.

Disheveled.—Person and quarters in a state of disarrangement and confusion.

Uncleanly.—Soiled or dirty. For these studies usually indicates presence of filth.

II. Motor Activity:

Destructive.—Tends to destroy various objects with which he comes in contact.

Dedifferentiated "push".—Abnormally directed drive which manifests itself in behavior of a more primitive type than that normally exhibited.

Hyperactive.—Active over and beyond normal limits.

Increased activity.—Sufficiently overactive to be considered outside of normal limits.

Quiet.—Moves about ward in a normal, purposeful manner. Not noisy.

Slow but restless.—Moves about more slowly than normal. Aimless ambling.

Procrastinates.—Moves about, but prefers to defer activity until a future time.

Responds slowly.—Little or no spontaneous activity and such as is elicited by stimulation is slowed.

Vegetates.—No spontaneous activity and practically none in response to such stimulation as speaking or shaking. May respond slowly by withdrawal from painful stimuli such as pin prick.

III. Mood:

Hilarious.—Boisterously merry; in exceedingly high spirits.

Ebullient.—Overflowing with enthusiasm and good spirits.

Easily stimulated.—Readily brought to laughter or smiles. As readily brought to tears. Indicates an instability of mood.

Euphoric.—Feeling of well-being, confidence, and optimism.

Cheerful.—Presenting an ordinary well-balanced mood. Not used in the sense of being elated, but as opposed to sad.

Unhappy.—Not cheerful. Dissatisfied.

Bored.—Wearied and annoyed through lack of interest.

Gloomy.—Downcast and cheerless.

Pessimistic.—Prone to look on the dark side.

Blue.—Melancholy.

Morose.—Sullen, sad.

III. Mood—Continued.

Depressed.—Cast down and dejected to a marked degree.

Weeping.—Sheds tears as a result of depressed mood and not necessarily because of any external stimulation.

Apathetic.—Indifference or lack of interest in surroundings due to extremely depressed state.

IV. Cooperation:

Unable to cooperate.—Cooperation is impossible due to state of excitement, distractions, and constant activity.

Ineffectual cooperation.—Patient makes some attempts to cooperate, but these are mostly fruitless because of excitability, distractability, and constant activity of patient.

Erratic cooperation.—Attempts to cooperate and at times may cooperate well, while at other times cooperation is poor.

Cooperates eagerly.—More than willing to cooperate in every way. Will go so far as to attempt to anticipate desires of the personnel.

Cooperative.—Follows directions and adheres to ward rules. Works cheerfully and willingly with ward personnel in the study and treatment of his case.

Perfunctory cooperation.—Cooperates half-heartedly, mechanically and without interest.

Grudging cooperation.—Cooperates reluctantly or unwillingly.

Poorly cooperative.—Degree of cooperation unsatisfactory due to general slowing down of the patient with loss of interest and prolonged reaction time.

Uncooperative.—Refuses or makes little or no attempt to cooperate because of loss of interest and general depression.

V. Speech:

Disconnected.—Speech is a jumble of words and phrases. Rapidly shifts from one idea to another, often in the middle of a sentence.

Silly.—Conversation is foolish and lacking in ordinary good sense. Speaks in connected sentences, however.

Garrulous.—Given to more or less continuous and tedious talking. Conversation makes sense.

Talkative.—Given to much talking.

Conversational.—Chats with acquaintances and personnel on the ward. Will talk in an animated manner about subjects of interest, but will also listen quietly while others are talking. Does not become irritating or boring by his talking.

Productions decreased.—Will carry on short conversation but not with much enthusiasm. Does more listening than talking.

Does not initiate conversation.—Speaks when spoken to, but does not spontaneously carry on a conversation. If asked a question will answer it adequately.

Monosyllabic responses.—Does not answer questions fully, but rather answers with "yes" or "no" or one or two syllables. There is often considerable delay between question and answer.

Unresponsive.—Will not speak when spoken to. May respond by a shake of the head or a frown but does no more than this.

VI. Herd:

Erotic.—Sensual or lustful in behavior toward those with whom he comes in contact.

Obnoxious.—Offensive and repelling in behavior.

VI. Herd—Continued.

Affectionate.—Behaving in an amatory manner. Has a tendency to attempt to fondle or place arm about acquaintances on ward.

Hearty.—Exceedingly cordial and rather demonstrative.

Gregarious.—Associates or mixes with the patient group freely, but in a reasonably reserved manner.

Companionable.—Associates with a few acquaintances on the ward but does not mix with the patient group as a whole.

Unsociable.—Does not mix with other patients. Does not repel friendly advances but responds very little and does not encourage further acquaintance.

Seclusive.—Behavior generally shut-in. Actively repels advances by other patients and makes no friendly contacts. Will walk about the ward some, however.

Withdrawn.—Remains in room. No longer moves about. Appears not even to notice other patients; in fact contact with other people appears nearly completely severed.

The attendants were carefully trained to observe the phenomena being studied and as soon as it was determined that they were sufficiently proficient to record reliable and accurate data they were given no further suggestions while the series of cases were being studied. No one else recorded any of the data except these specially trained individuals whose concepts of the terms employed were as nearly identical as possible. This was done in order that the observations would not be colored by any preconceived ideas in the minds of the investigators. The physical observations were made three times each day, as was described in Part II, and at these times the behavior of the patients since last observation was also recorded.

Five individuals were studied who received only morphine and 5 in whom, after being stable on morphine for at least 7 days, codeine was abruptly substituted and continued in maintenance doses for 10 days, at the end of which time all drug medication was abruptly and completely withdrawn. Data were collected on 16 patients, but because of gross personality defects, which were brought to light by means of independent examinations, all but 5 were discarded, since, while such defects did not significantly influence certain physiological changes, they would tend to invalidate data collected for the purposes of this study. The daily score was determined by adding the plus scores and the minus scores separately for the day in *each* category, thus obtaining the range of the daily swing from plus to minus. In order to obtain the entire picture of behavior, so far as it was studied, the daily plus scores in *all* categories were added together as were also the minus scores. The range from plus to minus thus determined was called the "total daily swing." The results of these studies were analyzed as to both the 6 individual categories and their total. Because the individual patient's average daily deviations were small, the sums of the three daily scores were used throughout.

Therefore, the data presented in figures 1 to 8 represent the group averages of the daily (or hourly) summed scores. Owing to the fact that changes take place rather rapidly during withdrawal, hourly observations were made for 48 hours in the same manner, except that the hourly scores in each category were added together to obtain the "total hourly swing."

Results

The scores for "appearance" are plotted in figure 1. In this case all daily scores were well on the minus side. It will be noted that there was a sharp rise in the curve, beginning on the second day of morphine stabilization and leveling off on the fourth day, only
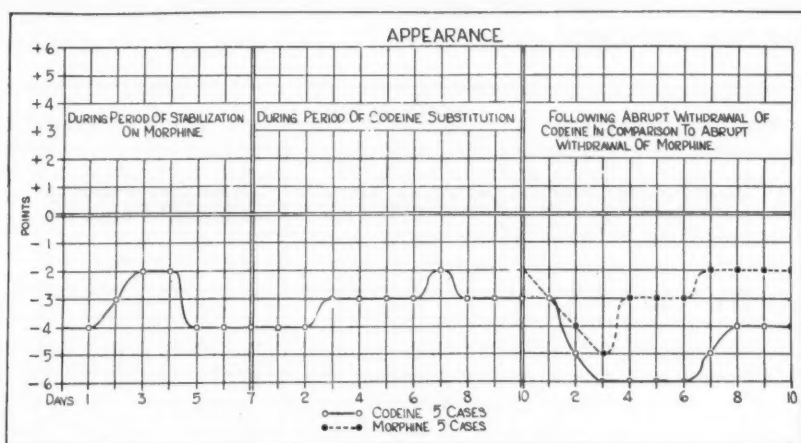
to fall to its original level on the fifth, this level being maintained through the second day of codeine administration and then rising again. These fluctuations cannot be adequately explained, but there are two possible interpretations, one being that, owing to the small series of cases, sharp fluctuations in the scores of the individual patients make themselves more apparent in the final average, and the other that, since the patients were on a physiologically stable dose in the case of both codeine and morphine, they were still un-stable so far as behavior was concerned. It has been our experience that appearance is one of the more sensitive indicators of the level of behavior. Keeping this latter observation in mind, the fact that the curve does not rise to the zero base line at its highest point is significant, since it indicates the emotional instability of the patients as a group. There is very little difference between the daily mor-phine scores and those for codeine. The scores obtained following abrupt withdrawal are plotted for both the codeine cases and the

morphine controls. It will be noted that no change occurred in the case of codeine during the first 24 hours. Following this, however, the drop was much more rapid and profound than in the case of morphine, and recovery was slower. It was not until the seventh day that the curve began to rise in the case of codeine, while with morphine the rise commenced on the third day. On the tenth day the codeine score was no higher than the lowest score obtained on any day while on drugs, while the morphine score was as high as the highest score obtained previously. It would appear, therefore, that insofar as appearance is concerned the effects of codeine substitution are practically no different than those of morphine administration in maintenance doses, but that the effects of codeine withdrawal are much more profound and prolonged than those of morphine withdrawal.
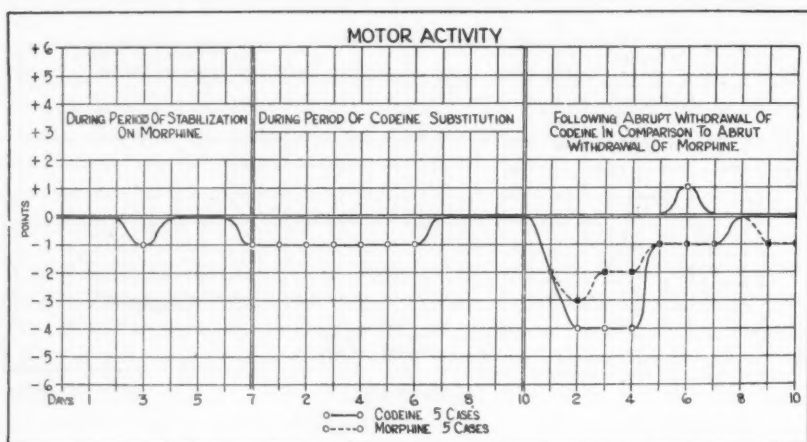

FIGURE 2.

Motor activity is shown in figure 2. There was practically no deviation from normal during the period of morphine stabilization. When codeine was substituted, however, the patients became more restless for a few days. Following withdrawal there was the same general trend as was observed in the "appearance" category. For the first 24 hours the changes were very similar in both the codeine and the control groups, but by the end of the second day the motor activity of the codeine patients was less than that of the morphine controls. The latter group began to show improvement on the third day, while the former showed none until the fifth, but then the rise was much more rapid, so that by the sixth day the scores were the same in both groups, and from that time on through the tenth day the patients who received codeine were the more active of the two groups.

Mood (fig. 3) remained within normal limits during the period of stabilization on morphine. Following codeine substitution there was a slight swing to the minus side on the second day, with return to normal limits on the fourth. This was probably due to the fact that the patients realized that they were receiving something besides morphine, which disquieted them, and also because the codeine dosage was not exactly adjusted to the patients' requirements during that time. Following withdrawal, the deviations in both the controls and the codeine groups were similar for the first 24 hours; but while the control group leveled off on the second day, the codeine patients continued in a downward direction until the third day, although the slope of the curve became less steep. Improvement began in both groups on the fourth day, and the two curves coincide by the fifth.
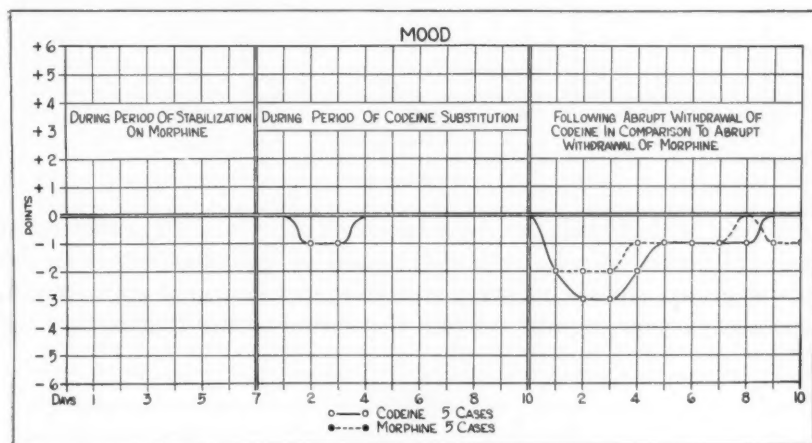

FIGURE 3.

Practically no change was found so far as cooperation was concerned when codeine was substituted for morphine (fig. 4). In both situations cooperation was within normal limits so long as narcotics were administered. It must be remembered, of course, that the patients realized that cooperation was expected of them, and they, therefore, made a special effort in this direction in order that they might obtain the most from their treatment. Following withdrawal, both the control and the codeine groups became less cooperative, the codeine group remaining cooperative for a longer period of time, however. This is probably explained by the fact that a longer period of time elapsed before the patients who had received codeine began to show evidence of abstinence. This period was sometimes as long as 36 hours. It is interesting to note that if the codeine curve were set over to the left the distance representing 1 day, the curves would be almost identical.

The patients were more talkative while on morphine, their average daily score being higher than after codeine was substituted (fig. 5). Except for the first day or two following the shift to codeine, however, oral productions were not decreased below the conversational level.
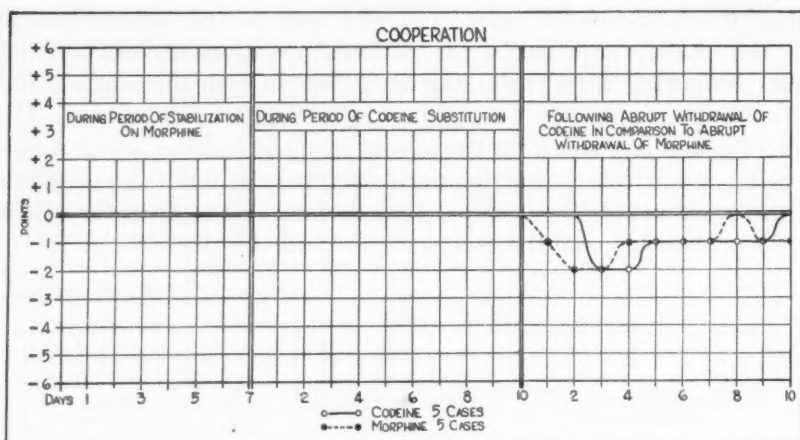

FIGURE 4.

Following withdrawal, the same sequence of events was noted as in other categories. Speech was diminished to a greater extent in the codeine group, and the upswing was delayed longer, but once started, it proceeded more rapidly. From the second to the fourth days the
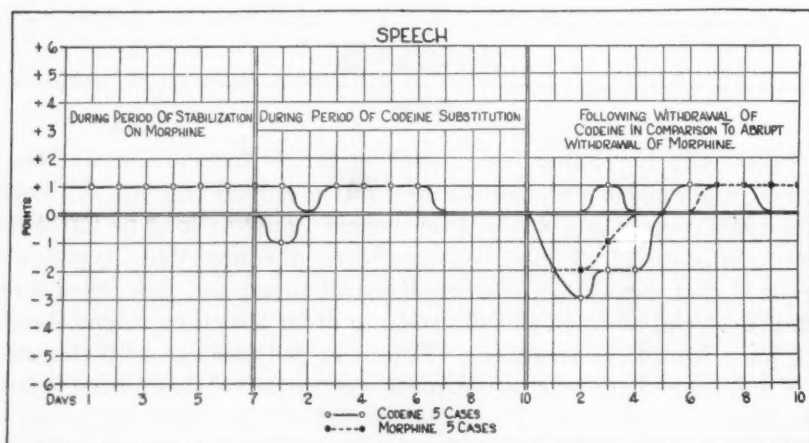

FIGURE 5.

patients received plus as well as minus scores, owing to the fact that, while they were disinclined to visit with other patients, they were more prone to complain to physicians and attendants about their physical discomfort.

Figure 6 illustrates the degree to which the patients bore one another's company during the period of observation. While they were stabilized on morphine there was a rather hearty association which changed within the first 24 hours after codeine was substituted. During the first 3 or 4 days the patients would associate with friends who had been on the ward with them throughout their stay, but they did not make friendly advances to others, especially newcomers. After about the fourth day they became more gregarious, but it could not be said that they were hearty in their associations. Following withdrawal the contrast between the codeine group and the morphine controls was rather striking. The control group became rapidly unsociable, the lowest scores being recorded during the first and second days; but within 4 days this had disappeared and they
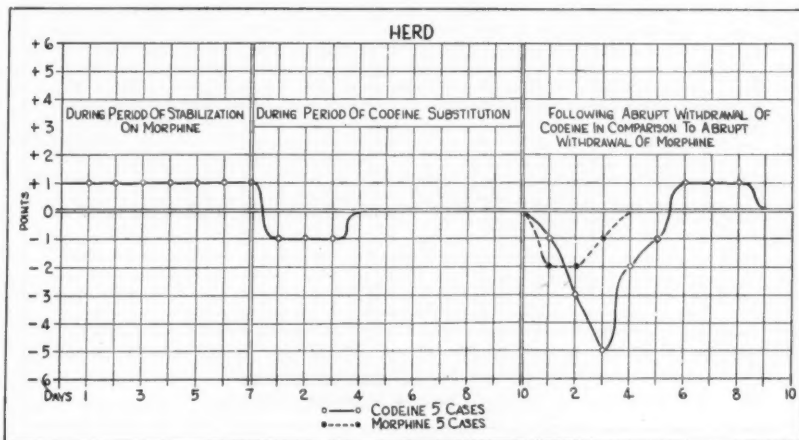

FIGURE 6.

were again mixing with the other patients in a normal fashion. The codeine group, on the other hand, became unsociable more slowly, so that the lowest scores were not recorded until the third day. These patients became seclusive and did not encourage any friendly advances. It was not until the sixth day that they again could be considered as mixing normally with other patients.

A study was made of the changes occurring in the first 48 hours following abrupt withdrawal of both morphine and codeine. The total hourly swing is plotted in figure 7. The observations of the first 8 hours are not plotted, since there was no appreciable change during that period. Changes in behavior began to be noticed between the ninth and tenth hours, and, contrary to what would be expected from studying the daily scores, was more pronounced at first in the cases which had been receiving codeine. By about the fifteenth hour, however, the changes observed in the morphine control group

had become the greater and remained so until well into the second day. The scores of the codeine group then became greater and at the end of 48 hours the curve still had not turned upward. One fact that must be kept constantly in mind in evaluating the results of the hourly observations is that all of the patients were apprehensive and some quite fearful following discontinuance of injections. They

TOTAL HOURLY SWING
FOLLOWING LAST DOSE
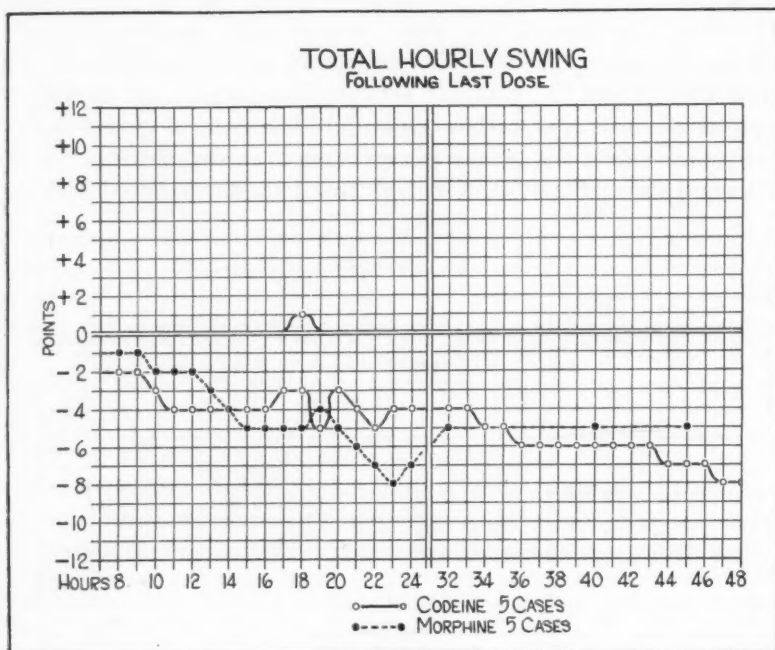
o——o CODEINE 5 CASES
•·····• MORPHINE 5 CASES

FIGURE 7.

knew that they would receive no more drugs and they were aware, through past experiences, of the inevitable result. The behavior of the individual members of the group varied according to the manner in which they met this difficult situation. Some were much more stoical than others, and the scores plotted in figure 7 represent the average of a rather wide range of figures.

The average scores of the total daily swing are given in figure 8. While there was a swing from plus to minus during the day, during the period of morphine stabilization, the plus scores tapered off to the vanishing point after codeine was substituted. There was rather a drop during the first day and a complete disappearance of plus scores by the end of the seventh day. There was also an initial increase in the minus scores with a gradual return to about the morphine level, which means that those aspects of behavior studied by us are more on the depressed side following codeine substitution.

Further, the range of swing became narrowed. Following withdrawal the codeine curve fell somewhat more gradually but to a lower level than did that for morphine, the latter reaching its lowest point on the second day and the former on the third. At the end of the fourth day the codeine curve, while starting upward, had still not risen to the lowest point reached by the morphine curve, and had not reached the level of the last day of codeine administration until the tenth day.
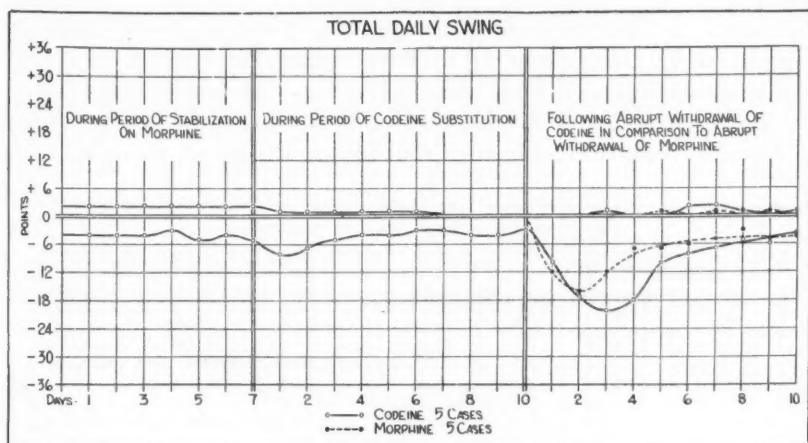

FIGURE 8.

A comparison of the curve representing total daily swing with that of the physical manifestations of abstinence is interesting. If the curves in figure 2, part II, are inverted (as has been done in fig. 9 of this section) and then compared with figure 8 of this section, some very interesting differences will be observed. It will be noted that whereas the physical manifestations of abstinence are much more pronounced for morphine, the reverse is true when certain aspects of behavior are studied, as has been described above. The slope of the curve following abrupt withdrawal is much more gradual in figure 8 for both morphine and codeine, but the codeine curve sinks to a lower level; in figure 9 the morphine curve reaches a much lower point than that for codeine. It would appear from a study of these curves that the effects of codeine on behavior and emotion are more profound than those of morphine, since the depression following abrupt deprivation is greater. The physical effects of morphine were more profound for the same reason.

If these effects of the two drugs are kept in mind, the statements quoted above, made by patients who have used codeine, may be much more easily understood.

Discussion

There appear to be two aspects to narcotic drug addiction, namely, physical and psychic, and in the usual addict these are almost indistinguishably interlaced. Whatever the original cause of addiction, the administration of drugs is continued because of psychic satisfaction as well as because of physical dependence upon the narcotic. It is this psychic element which is responsible for most of the relapses to drugs months or even years after dependence has been lost through withdrawal, in the case of physically healthy individuals. This alone can account for the resumption of a practice which results in physical dependence with the necessity of never being far from a source of supply, causes financial loss, social ostracism, and finally loss of freedom and of friends. The addict will admit that, while he may enjoy the physical sensation resulting from taking a dose of narcotics, this

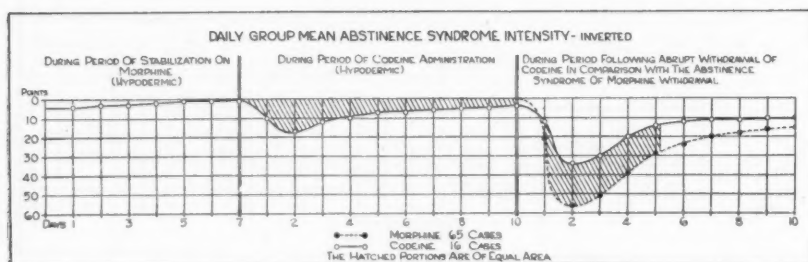DAILY GROUP MEAN ABSTINENCE SYNDROME INTENSITY - INVERTED

FIGURE 9.

is soon lost when dependence develops, and that a much more important factor predisposing to readdiction is the memory of the psychic effect of the drug. It would seem, therefore, that if a drug possessed less ability to produce psychic satisfaction as compared with morphine, it would be used to a much less extent. That codeine is such a drug can be deduced, not only from the studies described above, but also from the fact that patients are frequently willing to go through the discomfort of withdrawal rather than continue on codeine, even though physical dependence is fairly well supported. Further, while some individuals relapse to the use of drugs through codeine, they very quickly switch to morphine or heroin, even before dependence is built up.

In these investigations a small group of patients has been studied. The dangers of drawing conclusions from such a small number are realized, but, since the behavior of each member was very similar to that of the others, it was felt that the results obtained from a larger group would approximate those set forth here. Care was exercised to discard all cases in which the personality showed definite deviations from normal or in which there was evidence of somatic disease

which would possibly distort the picture. In exercising these precautions, the number of cases was necessarily reduced. The results clearly indicate, however, that the dosage of either morphine or codeine required for physiological stabilization is lower than that necessary to produce psychic satisfaction. While at first glance there seems to be little difference between the morphine and codeine curves, closer observation reveals that there is an abrupt drop and eventually a disappearance of the curve representing the plus scores in the case of codeine. The daily swing, therefore, is almost entirely on the minus side, which means that little or no psychic satisfaction was experienced. Kolb (4) has spoken of "positive" and "negative" pleasure to be derived from the use of narcotics, the former being that resulting from rising above the usual emotional plane which is probably experienced chiefly in the early states of addiction, and the latter being that which follows relief from anxiety or pain, which seems to be the principal type experienced once dependence is established. Using this concept we would say that, while there probably is some positive pleasure derived from morphine, there is definitely none obtained from codeine during maintained addiction. On the other hand, owing to the decrease in the ability to allay anxiety and an unpleasant emotional state, which the patients describe as an absence of "lift" or "kick," there is also a decrease in negative pleasure, since even a normal state of peace and calm cannot be attained. Under these conditions it might have been anticipated that there would be no scores above the zero base line on our graphs.

Codeine, therefore, seems to be an unsatisfactory drug from the standpoint of the addict because of the fact that its psychic effect is negative rather than positive. They are not "lifted up," which is nearly as undesirable as being "let down."

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(3) Kolb, Lawrence, and Ossenfort, W. F.: Treatment of drug addicts at the Lexington hospital. South Med. J., 31: 914 (August 1938).
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PART V. URINARY EXCRETION OF CODEINE

By Fred W. Oberst, *Biological Chemist, United States Public Health Service Hospital, Lexington, Ky.*

Various statements have appeared in the literature concerning the excretion of codeine, few of which are based on sound experimental evidence. Probably the earliest work is that of Tauber (*1*) in 1892, who reported that in dogs about 90 percent is excreted unchanged, some in the feces, but mainly in the urine. In 1903 Bouma (*2*) found no codeine dependence in dogs and concluded that there is no power of the organism to decompose this substance. He stated that four-fifths of the codeine injected is eliminated chiefly in the urine and a much smaller amount in the feces. He further reported that with continued administration of codeine the organism did not develop the ability to destroy it, which fact he believed explained the absence of addiction after the continuous administration of this drug.

Wolff (*3*), in 1938, stated that morphine introduced subcutaneously is mainly eliminated with the feces, whereas codeine is excreted chiefly in the urine. He probably based his statements on Tauber's and Bouma's work, for apparently he did not carry on any codeine or morphine excretion studies himself. He correlates the absence of real addiction with complete elimination of codeine by the following argument. When addiction does occur, the organism must first adjust itself to the chemical decomposition of the administered drug. The administered drug is eliminated completely during the initial doses, but as addiction develops the amounts of drug eliminated become less and less until finally little or none is excreted. This, he believes, perhaps affords a sign of addiction which may be detected by chemical means. He apparently discounted the work of Plant and Pierce (*4, 5*), Wolff, Riegel, and Fry (*6*), and Keeser, Oelkers, and Raetz (*7*), which appears to show that the addicted organism does not possess an increased capacity to decompose morphine.

Wolff also mentioned that codeine elimination in humans described as codeine addicts has not been investigated. It was then natural for him to speculate on what might happen if codeine were given to a person already addicted to morphine. He believed that it might be possible that such an organism had acquired the capacity to split off the methyl radical of codeine, thus liberating either morphine or a decomposition product of morphine which would act as the habit-forming substance. This view, he admitted, is only hypo-

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thetical and more experimental work must be done before definite conclusions can be drawn.

In 1913 Sollier (8) reported that the elimination of codeine in a man 72 years old taking 2 grams daily roughly follows the same course as that of morphine. A specimen of urine was examined before withdrawal treatment and a positive reaction for an alkaloid was obtained. This substance was soluble in ether, produced some of the reactions of morphine, but did not have reducing properties. In general, the chemical properties of this substance corresponded more closely with those of codeine than of morphine. He also stated that 25 days after withdrawal no alkaloid was found in the urine.

It can be seen from the foregoing review that very little is known about codeine excretion in humans. The present study was undertaken to determine the excretion of morphine and codeine in morphine addicts before and after the complete substitution of codeine for morphine. In addition there is included a study of the excretion of codeine in a patient who was addicted to codeine.

Experimental Procedure

Selection and management of subjects.—The routine management and care of the patients on whom these studies were made has been described in Part II. Eight morphine addicts with well-established physical dependence were stabilized on the minimum amounts of morphine necessary for physiological equilibrium. Four of these addicts were given morphine by mouth 1 to 5 days prior to the substitution of codeine given orally. Another 4 received both drugs subcutaneously. The excretion of the morphine in the urine of each man was determined daily for 2 to 10 days before codeine was substituted for morphine. Approximately five times as much codeine as morphine was required to maintain physiological stability. When morphine was administered orally, the amounts required were slightly greater, except in one case, than when administered subcutaneously.

Codeine excretion studies were carried out on one patient, a former morphine addict, who upon relapse chose codeine as the drug of addiction. He had used codeine continuously and exclusively for a period of 5 months prior to his admission to this hospital. At the time of his admission he claimed to be using 6 to 8 gr. of codeine daily. As this man was a codeine addict his stabilization was accomplished with codeine rather than morphine.

Urine analyses for morphine and codeine.—Twenty-four-hour specimens of urine preserved with 0.2 ml. of toluene were obtained daily from each patient. The morphine was extracted, purified, and determined by the method described by Oberst (9), using the colorimetric procedure. After codeine was substituted for morphine, the

urine was analyzed daily for morphine until it was morphine free. Analyses for codeine were begun on the day of substitution. Since no satisfactory method for the extraction, purification, and determination of urinary codeine has been found in the literature, complete details for the procedure are given.

A QUANTITATIVE METHOD FOR THE DETERMINATION OF CODEINE IN URINE

The method for extracting codeine from urine is quite similar to that for morphine (9), using a continuous liquid-liquid extractor. An accurately measured sample of urine, usually 80 ml., taken from a fresh 24-hour specimen is saturated with powdered sodium bicarbonate. It is then introduced into a liquid-liquid extractor previously set up with approximately 125 ml. of a mixture of one part ethyl alcohol (95 percent) and three parts chloroform, one-fourth of the amount being in the extraction chamber and the rest in the receiving flask containing 0.5 ml. of concentrated hydrochloric acid and one or two glass beads. The extraction is usually carried on for 2 hours at a temperature sufficient to cause ebullition of the solvent and allow the distillate to trickle slowly through the urine. Then the receiving flask is removed and the organic solvent evaporated to dryness on a water bath. The residue is dissolved in 10 ml. of 0.5 percent hydrochloric acid and is transferred to a 250 ml. separatory funnel. The flask is washed several times with small portions of the acid, each washing being added to the funnel. This solution is extracted once by shaking the funnel for several minutes with an equal volume of a mixture of one part ethyl alcohol and three parts chloroform. After the two immiscible liquids separate, the lower layer is drained off and discarded. The dilute acid solution remaining in the funnel is then saturated with powdered sodium bicarbonate. This solution is then extracted three times with equal volumes of the ethyl alcohol-chloroform mixture. The combined alcohol-chloroform extract, acidulated with 0.5 ml. of 0.5 percent hydrochloric acid, is evaporated to dryness in a small evaporating dish on a water bath.

This residue is dissolved in 2 to 5 ml. of water and transferred quantitatively to a 125-ml. cylindrical separatory funnel containing 6 gm. of washed permutit. By agitating the fluid several times in the course of 30 minutes, all of the codeine is combined with the permutit. The fluid is carefully removed by decantation, avoiding any loss of permutit, and is replaced three times with an equal volume of distilled water to wash the permutit free of interfering substances, the wash water being decanted and discarded each time.

The codeine is next separated and extracted from the permutit by the addition of approximately 2 ml. of saturated sodium bicarbonate and 25 ml. of the ethyl alcohol-chloroform mixture. After being

shaken a few minutes, the separatory funnel is clamped upright in a holder. The extraction solvent separates to the bottom, while the permutit and sodium bicarbonate solution float to the top. This makes it easy to drain off the ethyl alcohol-chloroform mixture into a beaker and then transfer it to an evaporating dish. This extraction is repeated three times. After each separation the organic solvent is added to the first portion. Approximately 0.5 ml. of 0.5 percent hydrochloric acid is added to the evaporating dish and the entire contents evaporated to dryness.

The final residue is dissolved in 1 or 2 ml. of water and is filtered through a small filter paper (approximately 25 mm. in diameter) into a suitable test tube (25×100 mm.). The dish is washed four times, each portion being filtered and added to the first filtrate. The total volume must not exceed 10 ml. One drop of 25 percent solution of potassium chloride and 0.5 ml. of 5 percent hydrochloric acid are added. Codeine is precipitated from this solution by the gradual addition of 2.5 ml. of 5 percent silicotungstic acid.

After leaving the tubes overnight in a refrigerator at approximately 8° C., the precipitate is filtered off with mild suction in a tared Gooch crucible. The precipitate is washed twice with 0.5 to 1.0 ml. portions of a filtered 0.5 percent solution of hydrochloric acid previously saturated with codeine-silicotungstic acid precipitate and finally dried at 103° C. to constant weight.

Discussion of method.—The codeine equivalent of a given weight of dry codeine-silicotungstic acid precipitate is slightly variable, depending on the amount of codeine present. This equivalent was determined for amounts varying from 0.46 mg. to 4.61 mg. codeine base. Known amounts of codeine hydrochloride were added to codeine free urine, which was then treated as described above. A graph, figure 1, was made by plotting amounts of codeine base against their corresponding weights of silicotungstic acid precipitate. These points follow very closely an empirical equation:

$$C = 0.180 + 0.404X - 0.00684X^2,$$

where C is the weight of codeine base and X the corresponding weight of codeine-silicotungstic acid precipitate.

Following the withdrawal of codeine the amount of the drug present in 80 ml. of urine was usually too low to yield a weighable precipitate. Under these circumstances 150 to 200 ml. of urine were extracted in a larger extractor, the extraction time being extended to 3 hours.

The presence of potassium chloride and hydrochloric acid in a codeine solution causes the codeine-silicotungstic acid precipitate to agglomerate, thus allowing it to be retained quantitatively on the

Gooch filter. Only mild suction can be used on the crucible with-
out danger of losing a portion of the precipitate. The crucible
should not be used more than twice without repacking it with fresh
asbestos. It is preferable that its weight does not exceed 12 to 13
grams when 0.5 to 5 mg. samples are to be weighed in it. In drying
the precipitate excessive rise in temperature must be avoided so as
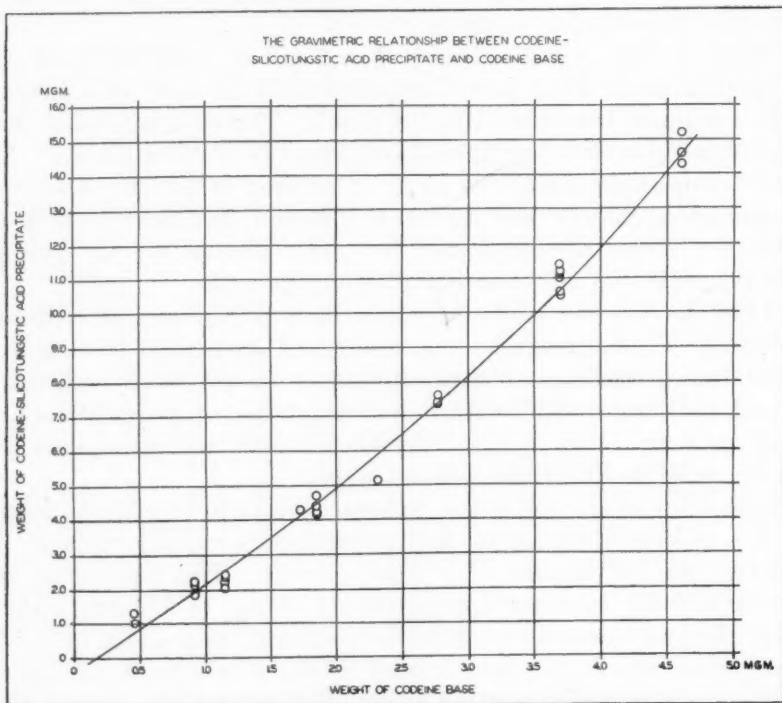not to cause decomposition of the precipitate.

FIGURE 1.—Curve is a plot of the equation $C = 0.180 + 0.404X - 0.00684X^2$. Points are
observed values.

The silicotungstic acid precipitate of morphine is considerably
more soluble than the corresponding codeine precipitate. With 0.2
mg. of morphine no precipitate was obtained. Treating 0.5 mg. of
morphine with silicotungstic acid in the presence of potassium chlo-
ride and hydrochloric acid gave a small amount of precipitate which,
after filtering and drying, was too low to be readily weighable. In
urine specimens where morphine, as well as codeine, may be present,
the concentration of morphine would have to exceed 0.5 mg. in a
given sample to have an appreciable effect on the weight of the
codeine-silicotungstic acid precipitate. The morphine concentrations
in the present studies were considerably less than this, and hence
did not interfere with the weighing of the codeine.

Most tobacco smokers excrete some nicotine in the urine. The urine from a number of smokers was tested by this method for the presence of a precipitate. Usually no precipitate was obtained, and when it was present the amount was not sufficient to cause an appreciable error.

Results

Table 1 summarizes the average daily amounts and the percentages of morphine and codeine excreted in the urine of 8 addicts during morphine administration and following substitution of codeine subcutaneously or orally. A study of codeine excretion in one patient who was addicted to codeine at the time of admission, and to whom no morphine was administered, is included. All morphine and codeine values are expressed in terms of the free bases.

TABLE 1.—*Comparison of urinary excretion of codeine with morphine (free alkaloid)*

Patient	Drug	Route	Number of days	Average urine volume	Average daily dose	Average daily excretion	Percentage excretion	Percentage range
				ml.	*mg.*	*mg.*		
I	Morphine	Subcutaneous	2	845	90.4	2.88	3.18	2.49– 3.87
	Do	Oral	5	755	102.3	1.67	1.66	.61– 2.21
	Codeine	do	10	950	483	22.2	4.58	3.46– 6.31
II	Morphine	Subcutaneous	7	1,494	101.1	3.11	3.16	2.08– 4.69
	do	Oral	1	535	90.4	1.55	1.72	
	Codeine	do	10	1,163	488	14.9	3.09	1.44– 5.82
III	Morphine	Subcutaneous	6	1,903	166.4	9.54	5.74	4.02– 6.97
	do	Oral	4	1,783	208.0	8.99	4.71	1.08–10.02
	Codeine	do	9	2,000	984	36.7	3.76	1.62– 8.35
IV	Morphine	Subcutaneous	5	2,271	120.3	12.52	10.41	7.54–12.55
	do	Oral	4	2,305	157.9	3.40	2.20	1.16– 4.96
	Codeine	do	8	2,635	764	34.4	4.58	1.59– 8.28
V [1]	do	Oral	7	1,685	930	53.5	5.78	4.52– 9.29
VI	Morphine	Subcutaneous	5	1,044	105.2	4.35	4.13	2.65– 5.16
	Codeine	do	10	1,030	563	29.8	5.29	2.22– 7.11
VII	Morphine	do	4	1,555	75.2	2.90	3.85	2.82– 4.87
	Codeine	do	10	1,228	338	22.2	6.56	2.07–10.50
VIII	Morphine	do	2	5,450	150.4	14.67	9.75	7.27–12.22
	Codeine	do	10	4,481	670	51.7	7.90	3.74–10.64
IX	Morphine	do	2	1,350	105.2	4.36	4.14	3.96– 4.31
	Codeine	do	9	716	539	20.5	3.79	1.40– 8.05

[1] Codeine addict.

During subcutaneous administration of either morphine or codeine, the percentage excretion in urine was higher than during oral administration, as shown in table 2. There was very little difference between the average percentage of morphine and codeine excretion when the drugs were administered subcutaneously, the values being 5.42 and 5.94 respectively. During oral administration the percent-

age of morphine excreted was a little lower than that of codeine, the values being 2.69 and 4.26 respectively.   The codeine excreted in the urine of the codeine addict was 5.78 percent, which is considerably higher than that of the other subjects receiving the drug orally. When the average values for this subject are omitted from the average for the entire group receiving codeine by mouth, the percentage values of codeine excreted drops to 3.98, which still is higher than that found for the morphine group.

TABLE 2.—*The percentage of morphine and codeine excretion during subcutaneous and oral administration*

Drug	Subcutaneous administration		Oral administration	
	Number of analyses	Average percent excreted	Number of analyses	Average percent excreted
Morphine_____	33	5.42	14	2.69
Codeine_____	39	5.94	44	4.26
			¹ (37)	¹ (3.98)

¹ The average values for the codeine addict are not included.

The highest average value for codeine excretion in any subject was 7.9 percent of the total intake.   This patient excreted an average of 51.7 mg. of codeine per day.   His daily urinary output was also by far the largest for the group, averaging 4,481 ml. per day.   His daily morphine output before substitution by codeine was higher than the average, varying from 7.27 to 12.22 percent.   On the other hand, the man with the lowest average urine output excreted a lower amount of codeine.   This patient averaged 716 ml. of urine per day for 9 days and excreted an average of 20.5 mg. of codeine per day, or 3.79 percent of the total intake.   Examination of other individual data reveals that a sudden increase in urine volume is usually accompanied by an increased morphine or codeine output.

Table 3 shows the daily analyses of urine from a morphine addict receiving morphine subcutaneously for 7 days and then orally for 1 day.   On the ninth day morphine was completely withdrawn, but an amount of codeine sufficient to satisfy the physical dependence was administered orally.   The amount of morphine excreted on the day the drug was given orally was considerably less than on any of the previous days.   Following the withdrawal of morphine and the substitution of codeine, morphine was found in the urine for 5 days.   The first day the value was a little higher than the highest values found before substitution.   Each succeeding day the amount excreted became less, until on the sixth day the amount present was too low for a positive identification.

TABLE 3.—*The excretion of morphine and codeine in the urine of a morphine addict during morphine administration and following substitution of codeine*

Date	Urine volume	Morphine base			Codeine base		
		In 24 hour urine	Amount administered	Percent excreted	In 24 hour urine	Amount administered	Percent excreted
October	*ml.*	*mg.*	*mg.*		*mg.*	*mg.*	
25	1,660	4.08	90.4 subcutaneous	4.52			
26	2,045	4.24	90.4 subcutaneous	4.69			
27	1,290	3.04	120.3 subcutaneous	2.53			
28	1,400	2.92	120.3 subcutaneous	2.43			
29	1,225	2.19	105.2 subcutaneous	2.08			
30	1,380	2.05	90.4 subcutaneous	2.27			
31	1,460	3.25	90.4 subcutaneous	3.59			
November							
1	535	1.55	90.4 orally	1.72			
2	1,860	4.72			8.1	563 orally	1.44
3	1,520	3.46			9.9	483 orally	2.04
4	740	1.31			7.8	483 orally	1.61
5	590	.7			9.4	483 orally	1.94
6	765	.5			17.5	483 orally	3.62
7	1,840				26.5	455 orally	5.82
8	1,145				13.3	483 orally	2.75
9	880				15.7	483 orally	3.25
10	1,395				19.0	483 orally	3.93
11	895				21.6	483 orally	4.47
12	920				6.4	0	
13	180				[1].6	0	

[1] Weight of precipitate was estimated.

On the first day of codeine administration 1.44 percent of codeine was found in the urine. The amount excreted each day thereafter was somewhat greater, the highest value being 5.82 percent on a day when there was a large urine output (1,840 ml.), following 3 days of low output (590 to 765 ml.). The average amount of codeine for the 10-day period was 14.9 mg. per day, which is 3.09 percent of the total intake. The codeine excretion in this man was the lowest among the 9 patients studied.

After withdrawal of codeine from this man the total amount present in the urine for the first day was 6.4 mg., which is less than half of the average amount excreted while on codeine. The second day only a trace of codeine was present, which is in accord with the usual findings. The last dose of codeine administered to this patient was at 10:00 p. m. The urine collection period ended at 7:00 a. m. of the next day, when he would have received the next dose of drug.

The daily excretion of codeine in the urine of the codeine addict receiving the drug orally is shown in table 4. The average daily excretion of codeine was 53.5 mg., the range being from 42.7 to 82.2 mg. The average percentage of codeine excretion in this case was 5.78 (range 4.52 to 9.29). The first day of withdrawal the amount of codeine excreted dropped to 15.8 mg. The second day it was 9.8 mg., the third day 2.4 mg., and the fourth day no codeine was found in the urine.

TABLE 4.—*The excretion of codeine in the urine of a codeine addict*

Date	Urine volume	Amount of codeine base administered orally	Amount of codeine base excreted	Percent of administered codeine excreted
Feb. 1939	*ml.*	*mg.*	*mg.*	
8	860	885	48. 6	5. 48
9	2, 045	885	82. 2	9. 29
10	1, 900	966	45. 3	4. 69
11	1, 680	966	43. 7	4. 52
12	1, 790	966	53. 7	5. 56
13	1, 770	966	58. 8	6. 09
14	1, 745	885	42. 7	4. 83
15	1, 685	0	15. 8	----------
16	1, 395	0	9. 8	----------
17	1, 495	0	2. 4	----------
18	1, 800	0	. 0	----------

Discussion

Methylation of the phenolic hydroxide of morphine produces a drug which is less effective in supporting preformed physical dependence to morphine. The relatively large quantity of codeine administered is apparently utilized and excreted just as efficiently as is morphine, for practically the same percentage of the amount administered is excreted unchanged in the urine. Wolff's hypothesis (*6*) that codeine is demethylated and excreted as morphine was not substantiated by this study. This point was especially investigated in the case of the codeine addict, in whom no evidence of demethylization was found. Furthermore, the daily successive decrease in the morphine content of the urine after codeine was substituted for morphine is strongly indicative that this change does not take place.

Apparently the amount of morphine stored in the body of a morphine addict is not very large. This is indicated by the fact that withdrawal symptoms usually appear in an addict about 12 hours after the last injection of morphine, and by the prompt drop in the amount excreted in the urine. When a sufficient amount of codeine is substituted for morphine, only mild withdrawal symptoms appear. The amount of morphine excreted under such conditions usually does not drop so rapidly, there being little or no diminution for the first day or two after the substitution. Considerable amounts of codeine are found in the urine on the first day after its administration. It appears that the codeine may have some sparing action on the morphine, allowing some of the stored morphine to escape unchanged into the urine. David's discussion of a paper by Himmelsbach (*10*), suggesting that the symptoms following codeine withdrawal might be due in part to the delayed excretion of this residual morphine, cannot be valid, since no morphine was found at any time after the first 3 to 5 days of codeine substitution. Further, withdrawal of

codeine from an unsubstituted codeine addict results in an abstinence syndrome strikingly similar to that resulting from withdrawal of morphine in a morphine addict.

It is unfortunate that it was not possible to follow the excretion of these drugs in the feces. However, it is unlikely that an appreciable amount of morphine or codeine is excreted by way of the bowel, since in a few isolated analyses of feces from stabilized addicts only traces of either morphine or codeine were found.

Just why the amounts of both morphine and codeine excretion in the urine should be higher in the subjects receiving the drug subcutaneously than in those receiving it orally cannot be stated at this time. The question naturally arises whether the absorption of the drug is complete when administered orally. To answer this adequately, additional work must be done on the excretion of the drug in the feces. On the other hand, it is also possible that a large amount of the drug may be destroyed either while passing from the intestinal tract to the liver or in the cells of the liver before becoming available to the general circulation. A smaller amount of the available drug in the body would naturally be reflected in a lower output in the urine.

The correlation of increased excretion of both morphine and codeine with increased urine volume is in accord with the observations of Pierce and Plant (5), who reported that diuresis in addicted dogs produced an increase in the excretion of morphine.

Summary

1. A gravimetric method for the determination of codeine in urine is described in detail.

2. Morphine and codeine excretion studies were made on 8 morphine addicts during morphine administration and following substitution of codeine. The elimination of codeine in the urine of a codeine addict is also reported.

3. During subcutaneous administration of either morphine or codeine, the percentage excretion in urine was higher than during oral administration.

4. There was little difference between the average percentage of morphine and codeine excretion when the drugs were administered subcutaneously, the values being 5.42 and 5.94, respectively.

5. During oral administration the percentage of morphine excreted was a little lower than that of codeine, the values being 2.69 and 4.26, respectively.

6. The average daily amount of codeine excreted in the urine of a codeine addict was 53.5 mg., which is 5.78 percent of the total amount administered orally.

7. Following the withdrawal of morphine and the substitution of codeine, morphine may be excreted for 3 to 5 days, the amount becoming less on each successive day.

8. After withdrawal of codeine the amount present in the urine for the first day was generally low. Frequently no codeine was found on the second day. The urine of the codeine addict was not free from codeine until the fourth day after withdrawal.

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PART VI. CLINICAL USE OF CODEINE IN THE CONTROL OF TUBERCULAR COUGH

By Lowrey F. Davenport, M. D., *Attending Specialist, United States Public Health Service, United States Marine Hospital, Boston (Chelsea), Mass.*

The Harrison Narcotic Act exempts preparations containing less than one-quarter grain (0.016 gm.) of morphine or one grain (0.065 gm.) of codeine per ounce. The average dose (one dram) of a cough syrup prepared under these exemptions contains not more than $\frac{1}{32}$ grain (0.002 gm.) of morphine, or $\frac{1}{8}$ grain (0.008 gm.) of codeine. However, when codeine is prescribed in tablet form for cough relief the usual amount is $\frac{1}{2}$ grain (0.032 gm.).

In view of the number of cases of codeine addiction found in the literature it seemed desirable to study this discrepancy and to redetermine the dosage required to control cough, since codeine is the drug most commonly used for this purpose.

Hatcher (*1*) states that in some cases $\frac{1}{30}$ grain (0.002 gm.) of morphine is sufficient to relieve cough. This result has been confirmed and the study extended to determine the minimal dose of codeine which is effective in controlling cough (*2*).

Methods

The present study was carried out on a series of advanced cases of pulmonary tuberculosis who complained of a disturbing cough. Since cough is a subjective complaint, data were obtained from observations made by the individual patients. These were supplemented with daily observations by the nurse and the physician in charge. Each patient was supplied with a mimeographed form for recording his impressions (see sample form).

Sample form

Date	Patient's notes on cough			Nurse's notes						
	Type: Dry? Productive?	Relief: Good? Fair? Poor?	Duration of relief	Dose	Time	Re-marks	Amount of spu-tum	Bowel move-ments	Sleep	Appe-tite

Although the patients and the nurses were familiar with the study program, changes in dosage were made without their knowledge. All tablets, including blanks of milk sugar, were identical in size, shape, and color. All medication was administered orally.

Although it is recognized that this subjective method is not entirely satisfactory, it was adopted only after attempts to obtain an objective measure of cough intensity had failed.

Results

The results of changing drugs and doses are summarized in table 1.

TABLE 1.—*Effect on cough of changing drug and dose*

Changing	Number reporting relief from cough as—			Number reporting duration of relief as—		
	Improved	Worse	No change	Increased	De-creased	No change
Codeine 0.010 gm. to milk sugar_____	0	9	3	0	9	3
Milk sugar to morphine 0.005 gm_____	9	0	3	9	0	3
Morphine 0.005 gm. to morphine 0.003 gm__	1	1	10	1	1	10
Morphine 0.002 gm. to codeine 0.010 gm.___	2	2	10	2	1	11

The duration of cough relief for various dosages of morphine and codeine is given in table 2.

TABLE 2.—*Average duration of relief*

Drug	Dose (gm.)	Duration of relief (hours)
Morphine_____	0.003	3⅔
Morphine_____	0.005	4½
Codeine_____	0.005	3½
Codeine_____	0.010	4

Quite uniformly satisfactory subjective relief from cough was obtained in the average patient with ⅙ grain (0.010 gm.) of codeine repeated every 4 hours if indicated.

Discussion

The results of this study indicate that the average tablet dose of codeine is unnecessarily large. During the past year the wards of the Middlesex County Sanatorium have been supplied with codeine in one-sixth grain (0.010 gm.) tablets. The sanatorium staff of 8 physicians from 8 different medical schools was given a free hand in increasing the dosage of codeine from one-sixth grain (0.010 gm.) to one-half grain (0.032 gm.) if it were thought desirable. Excluding dying patients and those suffering from hemorrhage, the dosage was increased to one-half grain in 21 of an approximate total of 475 patients treated from July 1, 1937, to January 1, 1938. Only 3 of these 21 cases reported satisfactory relief from cough with the three-fold increase in codeine dosage.

As a result of this study smaller doses of codeine are being administered at greater intervals than previously. This probably means a better understanding of cough control, and if, as seems probable, patients are just as comfortable as formerly, the intangible saving through avoiding the undesirable side actions of a narcotic is incalculable.

Cough control through the use of narcotic drugs is unnecessary in the large majority of patients suffering from pulmonary tuberculosis. Rest of the diseased lung, either physiological through rest in bed, or mechanical, by means of surgical compression, is the most desirable means of decreasing cough. Many patients learn to suppress voluntarily the nonproductive cough. In this sanatorium population, which usually averages 60 percent far advanced cases, less than 17 percent regularly required antitussic drugs. The detailed figures as of December 31, 1937, are:

		Percent
Total number of patients	378	100
Number receiving codeine	64	16.9
(a) Number requiring but 1 dose	29	7.7
(b) Number requiring 2 doses	12	3.2
(c) More than 2 doses	23	6.1

In this group 5 patients were receiving one-half grain (0.032 gm.) of codeine 3 times or more daily. One, a terminal case, has since died. Two were having severe hemoptyses, and in 2 the increased dosage was an unsuccessful attempt to control cough productive of more than 6 ounces of sputum in 24 hours.

Three types of cough are recognized in prescribing for tuberculous patients: (1) The moderately productive cough with sputum averaging less than 4 ounces in 24 hours; (2) the profusely productive cough where the expectoration may total a pint or more; and (3) the dry, irritating laryngeal cough.

A cough with moderate expectoration is well controlled with small doses of codeine. The medication may be needed only at bedtime, or the occasional case may require one-sixth grain (0.010 gm.) repeated every 4 hours.

The dry nonproductive cough is usually associated with laryngeal irritation, and in the tuberculous case is associated with tuberculous involvement of the larynx itself. Codeine and even morphine in large doses is never wholly effective. The laryngeal irritation, whether acute or tuberculous, is best treated by topical applications of medicated oil. Advanced cases of laryngeal tuberculosis may be treated by spray with a local anesthetic, preferably one of the synthetic preparations.

The profusely productive cough is a necessary evil, as it cleans the airways of secretions which might otherwise cause asphyxia. This

type of cough can be abolished only by a narcotic dose which will cause a central depression. The physician should reserve such large narcotic doses for only the terminal case where a physiologically vital reflex may be sacrificed for the comfort of the dying patient.

The use of the larger doses of codeine or morphine among ambulatory patients is wholly unjustified. At this sanatorium physical exercise is never permitted where medication is required for cough. The recumbent respiratory rate compared to that while walking gives ample evidence that pharmacological sedation is less effective than physiological rest. The physician who ignores this fact is guilty of negligence. He violates the same physiological principle as the physician might who prescribes a narcotic for relief of pain while allowing his patient to walk on a broken leg. Whether a broken lung with cough or a broken leg with pain, the underlying principle is the same.

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PART VII. THE SIGNIFICANCE OF CODEINE AS AN ADDICTING DRUG

Codeine (methylmorphine) was first isolated by Robiquet in 1332, but did not come into general clinical use until about 1880. Since then there has been wide divergence of opinion as to both its clinical value and its addiction liability. Its outstanding clinical usage has been for the relief of cough. Chronic cough, such as occurs in tuberculosis, often entails prolonged codeine administration, and this has led to discussions as to the danger of addiction resulting from such usage.

Although there is general feeling that codeine is not particularly effective against pain, Daland (1) stresses the fact that under proper supervision codeine can be used successfully against the pain of cancer in all but severe cases. The present-day trend toward codeine for the relief of both cough and pain is interpreted as a desire by physicians to use the safest available drug (from the addiction standpoint), which will produce the desired results. The studies reported in the previous sections were undertaken in an attempt to evaluate the significance of codeine as an addicting drug.

A comprehensive review of the literature revealed that codeine can and does produce addiction which is not readily distinguishable from addiction to morphine or heroin. However, codeine addiction is not common; only about 99 cases have been found in the literature, and only a few of these appear to have resulted solely from the use of codeine in the bona fide practice of medicine. It appears that the production of codeine addiction requires relatively larger amounts administered over longer periods of time than is the case with morphine. It appears, further, that the effect of codeine appeals to relatively few patients, but when it does they may prefer it to other addicting drugs.

The fact that codeine possesses addiction liability is further borne out by the fact that it has been shown to satisfy and support pre-established addiction to morphine. Even though the amount of codeine required to do this was 5.2 times greater than morphine, there was a definite loss in the intensity of physical dependence during the first few days following the substitution. It is recognized that a sudden switch from one drug to a chemically dissimilar one often entails readjustment in the biological process under consideration and that this shift undoubtedly contributed to the loss in in-

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tensity of physical dependence. Codeine will, however, support physical dependence for about two hours longer than morphine.

Since the abstinence syndrome which follows withdrawal of codeine substituted for morphine, although characteristic in its signs and symptoms, is measurably less severe than that of morphine, the question has been raised as to whether or not prolonged substitution of codeine would not result in a complete loss of physical dependence. That this is not true is borne out by many of the cases described in part I, and by the following patient:

Mr. R., a former morphine addict, after an abortive attempt at cure, finally completely substituted codeine for morphine of his own volition in September 1938. When he was admitted to this hospital 6 months later it was found that 1.2 gm. of codeine were required each day to satisfy his physical dependence on this drug. He was given no morphine. The abstinence syndrome which followed abrupt and complete withdrawal of codeine was as severe as in a patient undergoing morphine withdrawal, and differed only in that the onset was a few hours slower. It is significant that this patient used codeine to the exclusion of other drugs for 6 months when it actually cost him more than twice as much as morphine. He appears to be one of the few persons who was at least as well satisfied by codeine as by morphine.

Electroencephalographic studies indicate that in the main the cortical effects of codeine are similar to those of morphine. After several days of substitution of codeine the effect of the regular dose of this drug was to increase the amount of alpha activity and to decrease the alpha frequency. This is exactly the action of a regular dose of morphine given during preliminary stabilization on morphine.

The increase in bilateral asynchronism found during codeine administration may be due to the fact that the cortical readjustment to the new drug is not complete in 10 days, and hence does not represent an action differing essentially from that of morphine.

The fact that the cortical action of the regular doses of each drug gave analogous results, but at different levels, suggests that cortically the drug actions are similar, differing only in degree.

Studies of changes in certain aspects of behavior, considered to be objective manifestations of changes in the psychic state, indicate that codeine gives less psychic satisfaction than morphine. This is considered to be the reason that codeine is not particularly attractive to the average addict.

Most interesting was the finding that withdrawal of codeine causes a more profound effect on behavior than withdrawal of morphine. The reason for this is thought to be that the effects of codeine withdrawal were superimposed upon patients who had been psychically more or less dissatisfied for about 10 days.

The fact that approximately the same percentage of administered codeine as morphine is excreted indicates that the comparative ineffec-

tiveness of the codeine molecule in supporting addiction is not due to a failure of the organism to utilize the drug; rather that methylation of morphine attenuates its potency by about 80 percent. Furthermore, the fact that the same percentage is excreted probably indicates that the same mechanism is involved in the excretion of both morphine and codeine, and suggests that the action of codeine in other biological processes parallels that of morphine.

In view of the foregoing, we believe that the pharmacological effects of codeine are of the same nature but of a lower order than morphine in all of its characteristics. We recognize, of course, that the chemical modification has reduced some actions more than others. The reduction in addiction liability, although considerable, has not reached the point where this drug can be used liberally or indiscriminately over protracted periods. Studies on tuberculous patients indicate that codeine is commonly employed in very liberal amounts against cough. Attention has been called to the waste and inherent dangers in such practice.

In conclusion, a paraphrasing of a statement by Abraham Lincoln (2) completely expresses our views concerning the status of codeine as an addicting drug: "Codeine addiction does not result from the use of a bad thing but from the abuse of a very good thing."

C. K. HIMMELSBACH, M. D.   H. L. ANDREWS, Ph. D.
ROBERT H. FELIX, M. D.   F. W. OBERST, Ph. D.
LOWREY F. DAVENPORT, M. D.

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